Influence of Cytochrome P450, Family 2, Subfamily D, Polypeptide 6 (CYP2D6) Polymorphisms on Pain Sensitivity and Clinical Response to Weak Opioid Analgesics

Zalina ZAHARI1,2,* and Rusli ISMAIL2,3

1Department of Pharmacy, Hospital Universiti Sains Malaysia, Kelantan, Malaysia
2Pharmacogenetics and Novel Therapeutics Cluster, Institute for Research in Molecular Medicine (INFORMM), Universiti Sains Malaysia (USM), Kelantan, Malaysia
3Centre of Excellence for Research in AIDS (CERiA), University of Malaya, Kuala Lumpur, Malaysia

Full text of this paper is available at http://www.jstage.jst.go.jp/browse/dmpk

Summary: CYP2D6 polymorphisms show large geographical and interethnic differences. Variations in CYP2D6 activity may impact upon a patient’s pain level and may contribute to interindividual variations in the response to opioids. This paper reviews the evidence on how CYP2D6 polymorphisms might influence pain sensitivity and clinical response to codeine and tramadol. For example, it is shown that (1) CYP2D6 poor metabolizers (PMs) may be less efficient at synthesizing endogenous morphine compared with other metabolizers. In contrast, ultra-rapid metabolizers (UMs) may be more efficient than other metabolizers at synthesizing endogenous morphine, thus strengthening endogenous pain modulation. Additionally, for codeine and tramadol that are bioactivated by CYP2D6, PMs may undergo no metabolite formation, leading to inadequate analgesia. Conversely, UMs may experience quicker analgesic effects but be prone to higher mu-opioid-related toxicity. The literature suggested the potential usefulness of the determination of CYP2D6 polymorphisms in elucidating serious adverse events and in preventing subsequent inappropriate selection or doses of codeine and tramadol. Notably, even though many studies investigated a possible role of the CYP2D6 polymorphisms on pain sensitivity, pharmacokinetics and pharmacodynamics of these drugs, the results of analgesia and adverse effects are conflicting. More studies are required to demonstrate genetically determined unresponsiveness and risk of developing serious adverse events for patients with pain and these should involve larger numbers of patients in different population types.

Keywords: adverse events; analgesia; codeine; CYP2D6; opioid analgesics; pain; respiratory depression; tramadol

Introduction

Two percent of cytochrome P450 (CYP) enzymes in the human liver consist of cytochrome P450 2D6 (CYP2D6). CYP2D6 is involved in the metabolism of several drugs.1 Its activity exhibits genetic polymorphism, meaning that distinct population differences are apparent in its expression or activity. A drug that is metabolized through the CYP2D6 enzyme is referred to as a substrate of the enzyme. Increased CYP2D6 enzyme activity may result in faster metabolism and a shorter-than-expected half-life with potential loss of pharmacologic effect over time. In contrast, CYP2D6 enzyme inhibition may occur, resulting in a significant increase in circulating plasma concentration of a drug being metabolized by the enzyme. Consequently, the potential for increased side-effects or toxicity may occur at standard dosing regimens.2 Substrates are expected to be influenced by CYP2D6 polymorphisms and inhibitors are expected to influence other substrates of CYP2D6 if they are co-prescribed. CYP2D6 is also involved in the endogenous morphine synthesis pathway. Therefore, variations in CYP2D6 activity may impact a patient’s pain level and may contribute to interindividual variations in the response to opioids.3–11 Some drugs such as codeine are activated by CYP2D6 and poor metabolizers may get less pain relief. If we can prospectively identify patients at risk of severe toxicity, or
those likely to benefit from a particular treatment, we can reduce
the cost of treatment and increase the success of therapy more
quickly and certainly. Therefore, this review of the literature
was undertaken to identify evidence of the effect of CYP2D6
polymorphisms on pain sensitivity and response to opioid medi-
cations used for the treatment of pain including codeine and
tramadol.

CYP2D6 Gene

CYP2D6 or debrisoquine 4-hydroxylase is the most extensively
studied of the CYP enzymes because of the large geographical
and interethnic differences in the genetic polymorphism.12 CYP2D6,
as well as the other isoforms of cytochrome P450, are mainly
localised in the hepatocyte endoplasmic reticulum. Muratori
et al.13 provided convincing evidence that CYP2D6 is also present
on the hepatocyte plasma membrane. CYP2D6 is also expressed
in extrahepatic tissues including gut, kidney, lung, skin and brain.
Siegel et al.14 provided clear evidence of CYP2D6 expression
in certain regions of the human brain. Zhu et al.15 showed that
CYP2D6 is also present in immune cells (human white blood
cells).

CYP2D6 is involved in the biotransformation of many drugs
which predominantly act in the central nervous system (CNS),
including opioid analgesics, various psychotropic drugs and
denogogenous compounds, and the chemical toxicity of a reactive
intermediate.5,7,10,11,16–24

It is worth noting that the enzyme is also known to be involved
in the endogenous morphine synthesis pathway mainly in the
formation of dopamine from tyramine, and the conversion of
codeine to morphine.25,26 It has therefore been suggested that
variations in CYP2D6 activity may impact upon a patient’s
pain level and may contribute to interindividual variations in the
response to opioids.27–31

The CYP2D6 gene is mapped to chromosome 22q13.1. The
gene is located near two cytochrome P450 pseudogenes, CYP2D7P
and CYP2D8P.32 Alternatively, spliced transcript variants encoding
different isoforms have been found for this gene. The CYP2D6
genes consist of nine exons and eight introns. CYP2D8P is a
pseudogene and contains multiple deletions and insertions and
causes a highly disrupted open reading frame. CYP2D7P resembles
CYP2D6 more than it does CYP2D8P. Its coding sequence
indicates only a single inactivating mutation, an insertion of
T226 in the first exon. No specific mRNA product has, however,
been detected in the RNA from human livers suggesting that it
also is a pseudogene.32

CYP2D6 Polymorphisms

The gene encoding CYP2D6 is highly polymorphic. CYP2D6
allele nomenclature is available at http://www.cypalleles.ki.se/
cyp2d6.htm. The CYP2D6 allele subgroups are associated with
absent, decreased, normal or increased enzyme activity.33
Currently, more than 50 mutations and 100 alleles for CYP2D6
have been discovered, with many of them leading to the poor
metabolizer (PM) phenotype.34

Many different polymorphisms that affect CYP2D6 activity
have been reported in all parts of the world.12 These mutations
include genetic alterations that lead to over expression (gene
duplication), absence of an active protein product (null allele), or
production of a mutant protein with diminished catalytic capacity
(inactivating allele).

Individuals who express dysfunctional or inactive enzyme
molecules are considered PMs. The molecular genetic basis for the
PM status has been shown to be the occurrence of combinations of
any of a number of null alleles. So, a carrier of two null alleles is
considered a PM.2,23,35,36 At least 15 null alleles encoding non-
functional genes including CYP2D6*3, *4, *5, *6 and *14 have
been reported.

In addition to null alleles, there are also alleles that cause
diminished or altered drug metabolism leading to the production
of a low activity enzyme but not resulting in the PM status. So,
a carrier of two reduced function or one reduced and one non-
functional allele is considered an intermediate metabolizer (IM),
while a carrier of only one defective allele and one fully func-
tional CYP2D6 allele falls under the extensive metabolizer (EM)
phenotype.2,37

Extensive metabolizers are individuals who express enzymes
that have normal (extensive) activity, in whom the anticipated
medication response would be seen with standard doses of drugs.
A subject homozygous for the wild-type allele, CYP2D6*1 is
considered an EM. Among the EMs the metabolic rate can
vary considerably. In subjects homozygous for the active alleles,
CYP2D6 drugs are metabolized more efficiently than the hetero-
yzous genotypes (one active and one defective allele). In general,
the drug metabolism phenotype is determined by the number of
functional CYP2D6 gene present.36–38 At the opposite side of the
spectrum of EMs, the ultra-rapid metabolizer (UM) phenotype is a
consequence of a gene duplication (possessing multiple functional
copies of a single CYP2D6 gene).

An individual’s highest functioning CYP2D6 allele predicts his/
her phenotypic activity (for example and EM allele and PM allele
result in an EM phenotype, a UM allele and EM allele result in
a UM phenotype, and an IM allele and PM allele result in an IM
phenotype).2,35

Genetic polymorphism of the CYP2D6 may contribute to inter-
individual variations in plasma levels of opioid analgesics.39–43
The CYP2D6 genotype was found to be associated with variability
in opioid efficacy and toxicity.44–47 The CYP2D6 polymorphisms
were reported to be associated with specific phenotypes such as
pain sensitivity,27,28,48 schizophrenia,49,50 symptomatology of
patients with schizophrenia,51,52 side-effects of antipsychotics49,53)
and the risk of recurrence in breast cancer patients treated with
tamoxifen,54 but the evidence is conflicting.

Population Frequencies of the CYP2D6 Polymorphisms

CYP2D6*3 makes a minor contribution to the PM phenotype
in Caucasians, and is virtually non-existent in non-Caucasians.55
In normal Caucasians, Indo-Trinidadians, Afro-Trinidadians,
Mexican Americans, Mexican Mestizos and African Americans,
CYP2D6*3 frequency was about 0.2–2.0%53,36,56–63 and it was
rarely found in Asians.54–69

CYP2D6*4 is a non-functional allele that contributes to the
majority of PMs observed in Caucasians.59 CYP2D6*4 has
achieved a very high frequency, and homozygous individuals
are common.55 In most Chinese,65,66,70 Koreans,64 Malays71) and
Japanese,67,72 CYP2D6*4 almost always occurred at very low
frequencies of about 0–2.8%. CYP2D6*4 frequency was 7.6% in
African Americans,31 10.0% among 264 Mexican Americans,62
11.1% in a Mexican Mestizo population of 24361) and 1.9% in 103
Afro-Trinidadians.63 CYP2D6*4 was the most prevalent (11.7%)
null allele in the 167 Indo-Trinidadians.63 In Russians, the fre-
frequency was 18.1%, which is similar to other Caucasians like German, Italian, Swedish and Polish populations.\textsuperscript{36,56–59} It was found at slightly higher frequency in a Faroese population, 33.3% compared to other Caucasians.\textsuperscript{60} In South Indians and Malaysian Indians, the frequencies were 7.3%\textsuperscript{69} and 8.0%,\textsuperscript{68} respectively, which are higher than for other Asians, but lower than that observed in Caucasians, indicating a distinct genetic composition of the Indian populations.

Another allele causing poor metabolism is the deletion allele, \textit{CYP2D6}\textsuperscript{*5}. Generally, \textit{CYP2D6}\textsuperscript{*5} is found in the 0–7.0% allele frequency range in most populations and the allele was probably not an important cause of differences between populations in terms of \textit{CYP2D6} PM prevalences. The divergence in PM prevalence across populations would therefore probably be due to the differences in \textit{CYP2D6} frequencies although Japanese,\textsuperscript{67,72} Afro-Trinidadian,\textsuperscript{63} Korean,\textsuperscript{64} Chinese\textsuperscript{65} and Malay\textsuperscript{71} studies reported that \textit{CYP2D6}\textsuperscript{*5} (4.5–6.2%) was the most frequently occurring null allele.

Another allele causing PM is \textit{CYP2D6}\textsuperscript{*6}, which is rarely found. \textit{CYP2D6}\textsuperscript{*6} is found primarily in Caucasians, although with a low allele frequency when compared with the more common \textit{CYP2D6}\textsuperscript{*4} and \textit{CYP2D6}\textsuperscript{*5}\textsuperscript{36,55} \textit{CYP2D6}\textsuperscript{*6} was absent in most Chinese,\textsuperscript{65,66} Indo-Trinidadian,\textsuperscript{63} Afro-Trinidadian\textsuperscript{63} and Korean\textsuperscript{64} studies. In 360 Italians\textsuperscript{69} and 290 Russians\textsuperscript{59} \textit{CYP2D6}\textsuperscript{*6} was detected at frequencies of 1.4% and 1.2%, respectively, which are similar to that found in other Caucasian populations.\textsuperscript{36,60} In Mexican Americans and African Americans, \textit{CYP2D6}\textsuperscript{*6} frequency was 0.4%.\textsuperscript{33,62}

In Japanese, \textit{CYP2D6}\textsuperscript{*14} occurred at a frequency of 2.2%\textsuperscript{67} but occurred at a lower frequency (0.7%) in a study by Nishida \textit{et al.}\textsuperscript{72} It was found at a frequency of about 2.0% in Mainland Chinese\textsuperscript{66} and 0.5% in Koreans\textsuperscript{64} but none was found in Taiwanese Chinese,\textsuperscript{65} Caucasians,\textsuperscript{36} Mexican Americans,\textsuperscript{62} African Americans,\textsuperscript{61} Indo-Trinidadians,\textsuperscript{63} Afro-Trinidadians\textsuperscript{63} or South Indians.\textsuperscript{69}

Another \textit{CYP2D6} variant that clearly demarcates East from West is \textit{CYP2D6}\textsuperscript{*10}. \textit{CYP2D6}\textsuperscript{*10} has been investigated in many studies and found to occur at high frequencies in the East but to be rare or non-existent in the West.\textsuperscript{31,36,38,61–69,71,72} Although found at a percentage frequency of 38.0% in most Japanese studies,\textsuperscript{67,72} the rate was somewhat lower than the 56.0% reported in Mainland Chinese\textsuperscript{66} the 72.9% in Taiwanese Chinese\textsuperscript{71} and the 45.0% in Koreans.\textsuperscript{54} In South Indians and Malaysian Indians, it was found at the frequencies of 10.2% and 15.0%,\textsuperscript{68,69} which are very much lower than for other Asians like Japanese, Chinese, Malays and Koreans. The lower frequency of this allele highlights the distinctive nature of this ethnic group.\textsuperscript{58,68} In non-Asian studies, \textit{CYP2D6}\textsuperscript{*10} frequencies were generally low. In a study in Caucasians by Sachse \textit{et al.}\textsuperscript{36} \textit{CYP2D6}\textsuperscript{*10} occurred at a frequency of 1.5% among the 589 Germans studied. It was found at slightly higher frequency in Russians, namely 4.1%.\textsuperscript{58} Lopez \textit{et al.}\textsuperscript{61} determined an allelic frequency of 12.6% for \textit{CYP2D6}\textsuperscript{*10} in Mexican Mestizos which is higher than in Mexican Americans (2.8%)\textsuperscript{52} and African Americans (2.7%).\textsuperscript{63} \textit{CYP2D6}\textsuperscript{*10} occurred at a frequency of 2.9% in Afro-Trinidadians and 5.1% in Indo-Trinidadians.\textsuperscript{63}

The \textit{Z}-allele, \textit{CYP2D6}\textsuperscript{*17}, is a novel mutant African allele associated with reduced enzyme activity. It is common among Zimbabweans\textsuperscript{74} but it has not been widely studied in other populations such as Caucasians. \textit{CYP2D6}\textsuperscript{*10} occurred at a frequency of 16.5% in Afro-Trinidadians.\textsuperscript{63} The \textit{CYP2D6}\textsuperscript{*17} frequency in Mexican Mestizos was 1.7%\textsuperscript{61} which is higher than in Mexican Americans (0.2%).\textsuperscript{62} It was not found in a Japanese study,\textsuperscript{67} in Indo-Trinidadians\textsuperscript{63} or in Koreans.\textsuperscript{64} In Malaysian Indians and Malaysian Malays, the frequencies were 1.0% and 0.5%, respectively.\textsuperscript{68,71} \textit{CYP2D6}\textsuperscript{*17} was absent in South Indians, reflecting a degree of similarity in genetic composition with other Asians like Chinese and Koreans.\textsuperscript{69}

\textit{CYP2D6}\textsuperscript{*9} occurred at frequencies of 1.8% and 0.8% among 589 Germans and 309 Faroese, respectively.\textsuperscript{36,60} In Mexican Americans, the frequency was 1.1%\textsuperscript{62} and was 1.2% in African Americans.\textsuperscript{33} \textit{CYP2D6}\textsuperscript{*9} frequency was 0.3% in Indo-Trinidadians.\textsuperscript{63} In Malaysian Indians and Malays, the frequencies were 1.0% and 3.3%, respectively.\textsuperscript{68,71} The mutation was, however, not detected in the 180 Taiwanese Chinese studied by Liou \textit{et al.}\textsuperscript{65} or 400 Koreans\textsuperscript{64} and Afro-Trinidadians.\textsuperscript{63}

Although the majority of the population are EMs, the \textit{CYP2D6} genotypes are relatively heterogeneous, with predicted metabolic capability that ranges from UM to PM. About ten percent of Caucasians are PMs\textsuperscript{2,73} and a lower prevalence of PMs is found in other populations.\textsuperscript{12} The frequency of UMs varies between populations ranging from 1.0% to as high as 29.0% in different populations.\textsuperscript{12} About one-third of Asians showed genotypes that predicted an IM phenotype.

Jannetto and Bratanow\textsuperscript{76} demonstrated that the prevalence of \textit{CYP2D6} polymorphisms in the population undergoing pain management was not statistically different from that of the general population. The majority of their chronic pain patients (54.0%) were EMs; 41.0% were IMs and 5.0% PMs. Most of the patients enrolled were Caucasians (90.0%). The allele frequency of \textit{CYP2D6}\textsuperscript{*10} in Chinese and Malaysian patients with acute pain after major abdominal surgery and orthopedic surgery were comparable to previous data in the general population.\textsuperscript{44,77} The allelic frequencies for \textit{CYP2D6}\textsuperscript{*3, *4, *5, *6, *7, *8, *9 and *11} in 81 German Caucasians chronic pain patients treated with tramadol did not differ from those in the general population.\textsuperscript{78}

\textbf{Association of the \textit{CYP2D6} Polymorphisms with Pain Sensitivity}

The variability in opioid drug requirements is a reflection of inherent pain sensitivity that is related to genetic factors regulating their pharmacokinetics (metabolizing enzymes, transporters) and pharmacodynamics (receptors and signal transduction elements).\textsuperscript{79} Polymorphisms in genes that are involved in the endogenous morphine synthesis pathway predict variation in pain sensitivity. The endogenous morphine co-localises with mu-type opioid receptors in various parts of the brain stem. Endogenous morphine, like endorphins and enkephalins, may be involved in supraspinal nociception modulation.\textsuperscript{80} While the effects of \textit{CYP2D6} polymorphisms on pain medication metabolism have been investigated, to the best of our knowledge, there are very few studies that focus on the association of \textit{CYP2D6} and pain modulation. Studies showed that \textit{CYP2D6} polymorphisms may impact pain sensitivity.\textsuperscript{27,28,48}

Guarna \textit{et al.}\textsuperscript{81} investigated the effects of depletion of endogenous morphine on nociceptive transmission using a hot plate test. Antinociception was seen as increased latencies to the responses evaluated while increased nociception was seen by shorter latencies. They demonstrated the presence of naturally occurring morphine alkaloid in the mouse brain and observed...
that endogenous morphine immunoneutralization decreased thermal response latency and attenuated the antinociceptive effect of the mu selective agonist DAMGO ([D-Ala2, N-MePhe4, Gly-o1]-enkephalin). Therefore, depletion of endogenous morphine increased nociceptive transmission, suggesting that endogenous morphine may play a role in the modulation of thermal nociception.

CYP2D6 is a candidate gene with potential importance for nociceptive responsivity because it has been found to be involved in the endogenous morphine synthesis pathway mainly in the formation of dopamine from tyramine, and the conversion of codeine to morphine.\(^25,26\) It was hypothesized that CYP2D6 PMs may have a defect in the final step of a possible endogenous morphine synthesis in the brain.\(^48\) It was postulated that the CYP2D6 PM may be less efficient at synthesizing endogenous morphine compared with other metabolizers, similar to the role CYP2D6 has demonstrated in exogenous opioid metabolism. Poor metabolizers therefore have lowered endogenous morphine levels, thus weakening endogenous pain modulation. As a possible outcome of this down-regulation, patients experience acute severe pain more frequently.\(^28\) The finding of increased peak pain ratings and area under the pain rating-time curve in CYP2D6 PMs\(^48\) supported the hypothesis of lowered endogenous morphine levels associated with the CYP2D6 polymorphisms.

On the other hand, CYP2D6 UMs may be more efficient at synthesizing endogenous morphine compared with other metabolizers, thus strengthening endogenous pain modulation. As a possible outcome of this, less exogenous morphine is required for pain control.\(^27\)

Sindrup et al.\(^48\) examined the association between the CYP2D6 polymorphisms and two phasic (pain thresholds to heat and pressure) and one tonic (cold pressor test) experimental pain responses in a large sample of healthy Danish young adults \((n = 176)\). They found that the CYP2D6 phenotype was associated with cold pressor-induced pain responses. CYP2D6 PM exhibited less tolerance to tonic pain (higher peak pain ratings and area under the pain rating-time curve during 2 min) compared with EMs. Therefore, CYP2D6 PMs had higher sensitivity to pressure pain compared with EMs. In term of heat pain and pressure pain response, no main effect of the CYP2D6 phenotype was observed. Neither pain detection nor pain tolerance thresholds differed significantly between EMs and PMs.

This association was confirmed in another study by Yang et al.\(^29\) They studied 236 patients from the United States of America to investigate the consequences of the CYP2D6 genetic polymorphisms on the development of acute severe post-operative pain in female surgical patients immediately after general anesthesia. They found that the incidence of acute severe post-operative pain (linear analog pain scores \(\geq 8\)) was more frequent in patients with the CYP2D6 PM genotype, 71.0%, compared with 28.0% in IMs, 26.0% in EMs, and 27.0% in UMs. The overall association between metabolizer groups and severe post-operative pain was significant \((p = 0.023)\). PMs were significantly more likely to suffer from severe post-operative pain than IMs, EMs, or UMs \((p = 0.007, 0.002, and 0.050, respectively)\). This result suggested that the CYP2D6 PMs had higher pain sensitivity compared with those other CYP2D6 metabolizer genotypes, thus extending the previous findings of increased pain perception in PMs obtained using psychophysical responses to experimental pain models by Sindrup et al.\(^48\).

The results of the studies by both Sindrup et al.\(^48\) and Yang et al.\(^29\) are thus compatible with the hypothesis that PMs have a defect in the final step of a possible endogenous morphine synthesis in the brain. The final step in the biosynthesis of morphine is an \(O\)-demethylation of codeine. Alternative explanations, however, such as CYP2D6 catalysis of other metabolic processes or the mutation of the gene regulating CYP2D6 affecting a neighboring gene involved in pain modulation, may apply.

This association was contradicted by Candiotti et al.\(^27\) who found that the CYP2D6 PM genotype was not associated with increased pain sensitivity. One hundred forty-two women with mixed ethnicity (Black, Hispanic, White and others), who had undergone elective surgery and had adequate pain and morphine data (defined as patients who received only morphine for pain post-operatively and had at least 4 h of data collection) were included in the study. The study group was divided, based on morphine consumption, into two subgroups: low morphine consumers (LMC) \((\leq 10 \text{ mg/4 h}, n = 80)\) and high morphine consumers (HMC) \((> 10 \text{ mg/4 h}, n = 62)\). The CYP2D6 PM genotype frequency did not demonstrate a significant difference between the LMC and HMC groups. They also noted no significant differences between LMC and HMC groups in terms of frequency of the IMs or EMs. Therefore, the genotypes are not differentially represented between the LMC and HMC for those groups.

A possible explanation was that PMs have developed alternative pathways to produce or regulate endogenous morphine, limiting the phenotypic importance of the PM in pain modulation. Zhu et al.\(^25\) showed evidence that another pathway for morphine synthesis exists, via L-DOPA (3,4-dihydroxy-L-phenylalanine), demonstrating an intersection between the dopamine and morphine pathways. However, they demonstrated that CYP2D6 UMs required less morphine in the acute post-operative period compared with other CYP2D6 metabolizer groups. They noted that CYP2D6 UMs occurred more frequently in the low morphine consumer (LMC) group than the high morphine consumer (HMC) group. The hypothesis of the study was that the variability in opioid drug requirements is a reflection of inherent pain sensitivity. So, one possibility is that CYP2D6 UMs may have higher efficiency in synthesizing endogenous morphine compared with other metabolizers, thus increasing endogenous pain modulation. As a possible outcome of this upregulation, less exogenous morphine is required for pain control.

Table 1 summarizes the studies associating CYP2D6 polymorphisms with pain sensitivity. Even though only three studies have been reviewed, in total the studies have raised a significant question about the potential role of the CYP2D6 polymorphisms in pain sensitivity without reaching a clear resolution. Thus, the association between pain sensitivity and CYP2D6 polymorphisms remains controversial. Further studies are necessary to evaluate the results of these association studies between CYP2D6 polymorphisms and pain sensitivity.

**CYP2D6 Polymorphisms and Response to Drug Treatment and Side-effects**

Although the pharmacokinetic consequences of CYP2D6 polymorphism are relatively well documented for a number of CYP2D6 substrates, its clinical impact with respect to therapeutic response remains scanty. It has been shown that CYP2D6 polymorphism determines the effects of weak opioid analgesics such as codeine and tramadol. In the case of the elimination of a
drug that is highly dependent on CYP2D6, a lower clearance of this compound is seen in the PMs than the EMs. PMs may have higher plasma concentrations of and more side-effects to opioid analgesics. On the other hand, UMs could experience no analgesic effect or no pain relief, subsequently leading to therapeutic failure. At the same dosage PMs achieve higher steady state plasma drug levels than EMs due to their reduced metabolic capacity and are therefore more prone to develop side-effects. For prodrug opioids that need to be bioactivated by CYP2D6 into active metabolites, PMs may undergo no metabolite formation, leading to inadequate analgesia. Conversely, UMs may experience quicker analgesic effects but are prone to higher mu-opioid-related toxicity. Nonetheless, there should be more caution over potential problems when codeine and tramadol are concomitantly prescribed with inhibitors or inducers of CYP2D6 or other enzymes that are involved in its metabolism such as cytochrome P450 3A4 with inhibitors or inducers of CYP2D6 or other enzymes. When codeine and tramadol are concomitantly prescribed the plasma concentration of two other important active metabolites, morphine-6-glucuronide (M6G) and normorphine (NM), was significantly different between EMs and PMs. Eckhardt et al.84 found that EMs had higher concentration of the codeine dose converted to morphine and its metabolites than PMs (3.9% vs. 0.17%). Recently, Kircheiner et al.86 showed that the areas under the plasma concentration vs. time curves (AUCs) of morphine after codeine intake were increased by 2100% in EMs compared to PMs (11 vs. 0.5 μg.h/L).

It is increasingly recognized that the analgesic effect of codeine among healthy volunteers in experimental pain settings is not mediated by the parent drug, but the corresponding morphine metabolite.85,84,88 Previous studies have generated consistent results regarding the influence of the CYP2D6 PM phenotype on codeine analgesic effects where they found decreased or no analgesia among PMs compared to EMs.83,84,88

Desmeules et al.83 found that both subjective and objective pain threshold responses to selective transcutaneous nerve stimulation in PMs were not affected by codeine compared to a placebo. No effect of codeine in any of the pain tests was observed in the PMs (the cold pressor test and pain thresholds for heat and pressure stimulation).83 PMs also did not show an analgesic effect even after a high dose of codeine (170 mg) compared to a placebo.83

In terms of opioid related side-effects of codeine, controversial results have been shown regarding the impacts of the CYP2D6 PM phenotype on codeine pharmacodynamics among healthy volunteers.82-89 Desmeules et al.83 determined the impact of genetic variability in CYP2D6 function on codeine biotransformation. EMs (17.9 nmol/L) had substantially higher plasma morphine concentrations than PMs (0.6 nmol/L). This observation was confirmed by Yue et al.80 PMs also had low concentrations of two other important active metabolites, morphine-6-glucuronide (M6G) and normorphine (NM).80 Later, Caraco et al.82 reported that EMs had almost 200-fold greater codeine metabolic clearance by O-demethylation than PMs.

Mikus et al.87 reported that area under the serum concentration-time curve, 27.8 ± 16.0 vs. 1.9 ± 0.7 pmol.h/mL and total amount of morphine excreted in urine, 0.160 ± 0.036 vs. 0.015 ± 0.007 μmol were significantly different between EMs and PMs. Eckhardt et al.84 found that EMs had higher percentage of the codeine dose converted to morphine and its metabolites than PMs (3.9% vs. 0.17%). Recently, Kircheiner et al.86 showed that the areas under the plasma concentration vs. time curves (AUCs) of morphine after codeine intake were increased by 2100% in EMs compared to PMs (11 vs. 0.5 μg.h/L).

Table 1. Association studies of CYP2D6 polymorphisms with pain sensitivity

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Number of subject, N</th>
<th>Type of pain</th>
<th>Result</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>Danish</td>
<td>176</td>
<td>Two phase (pain and cold pressor induced pain)</td>
<td>PMs had higher sensitivity to pressure pain than EMs (less tolerant to tonic pain)</td>
<td>48</td>
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<tr>
<td></td>
<td>PM = 82</td>
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<td>A higher fraction of poor metabolizers prematurely withdrew their hand from the ice water during the cold pressor test due to intolerable pain (32.0 vs. 18.0%, p = 0.0545)</td>
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<td>EM = 94</td>
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<td>No association (two phase pain-pain detection and pain tolerance thresholds)</td>
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<tr>
<td>Mixed</td>
<td>142</td>
<td>Post-operative pain</td>
<td>UMs had lower pain sensitivity compared with other CYP2D6 metabolizer groups</td>
<td>27</td>
</tr>
<tr>
<td>(Black, Hispanic,</td>
<td>PM = 7</td>
<td></td>
<td>(UMs required less morphine)</td>
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<td>White, others)</td>
<td>IM = 23</td>
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<td>No significant difference in PM, IM, and EM frequencies in LMC compared with</td>
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<td></td>
<td>EM = 104</td>
<td></td>
<td>HMC (the PM, IM, and EM CYP2D6 genotype may not affect pain modulation)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>UM = 8</td>
<td></td>
<td></td>
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<tr>
<td>Mixed</td>
<td>236</td>
<td>Post-operative pain</td>
<td>PMs more likely to suffer from severe post-operative pain than other CYP2D6 metabolizer groups</td>
<td>28</td>
</tr>
<tr>
<td>(Black, Hispanic,</td>
<td>PM = 14</td>
<td></td>
<td>(UMs required less morphine)</td>
<td></td>
</tr>
<tr>
<td>Caucasian, others)</td>
<td>IM = 31</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>EM = 180</td>
<td></td>
<td>(UMs required less morphine)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>UM = 11</td>
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PM, poor metabolizer; IM, intermediate metabolizer; EM, extensive metabolizer; UM, ultra-rapid metabolizer; LMC, low morphine consumer; HMC, high morphine consumer.

Table 2. Polymorphism studies of CYP2D6 with pain sensitivity

<table>
<thead>
<tr>
<th>Type of pain</th>
<th>Result</th>
<th>Reference</th>
</tr>
</thead>
</table>
| Two phasic (heat and cold pressor-induced pain) | PMs had higher sensitivity to pressure pain than EMs (less tolerant to tonic pain) | 48
| Post-operative pain | UMs had lower pain sensitivity compared with other CYP2D6 metabolizer groups (UMs required less morphine) | 27
| Post-operative pain | PMs more likely to suffer from severe post-operative pain than other CYP2D6 metabolizer groups | 28

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<table>
<thead>
<tr>
<th>Study population</th>
<th>CYP2D6 polymorphism, N</th>
<th>Variable</th>
<th>Result</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy volunteers (Switzerland)</td>
<td>8</td>
<td>Plasma morphine concentrations <em>(C_{max})</em></td>
<td><strong>EMs &gt; PM</strong>&lt;br&gt; (Selective transcutaneous nerve stimulation)&lt;br&gt; Codeine significantly increased pain thresholds compared to placebo <em>(p &lt; 0.001)</em> in EMs&lt;br&gt; No significant analgesia was detected in PM</td>
<td>83)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Subjective and objective pain thresholds</td>
<td></td>
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<tr>
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<td><strong>EMs &gt; PM</strong>&lt;br&gt; (Selective transcutaneous nerve stimulation)&lt;br&gt; Codeine significantly increased pain thresholds compared to placebo <em>(p &lt; 0.001)</em> in EMs&lt;br&gt; No significant analgesia was detected in PM</td>
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<td></td>
<td></td>
<td>Morphine Metabolites</td>
<td><strong>EMs (detected) and PMs (not detected)</strong>&lt;br&gt; PMs had low concentrations of M6G and NM</td>
<td>89)</td>
</tr>
<tr>
<td>Caucasian healthy volunteers (Sweden)</td>
<td>14</td>
<td>Morphine Metabolites</td>
<td><strong>EMs (detected) and PMs (not detected)</strong>&lt;br&gt; PMs had low concentrations of M6G and NM</td>
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<td></td>
<td>Codeine metabolic clearance by O-demethylation</td>
<td><strong>EMs (detected) and PMs (not detected)</strong>&lt;br&gt; PMs had low concentrations of M6G and NM</td>
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<td></td>
<td></td>
<td>Respiratory, psychomotor and pupillary effects of codeine</td>
<td><strong>EMs (detected) and PMs (not detected)</strong>&lt;br&gt; PMs had low concentrations of M6G and NM</td>
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<td></td>
<td></td>
<td>Morphine and morphine metabolates</td>
<td><strong>EMs (detected) and PMs (not detected)</strong>&lt;br&gt; PMs had low concentrations of M6G and NM</td>
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<td>Codeine metabolic clearance by O-demethylation</td>
<td><strong>EMs (detected) and PMs (not detected)</strong>&lt;br&gt; PMs had low concentrations of M6G and NM</td>
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<td>Morphine and morphine metabolites</td>
<td><strong>EMs (detected) and PMs (not detected)</strong>&lt;br&gt; PMs had low concentrations of M6G and NM</td>
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<td>Codeine metabolic clearance by O-demethylation</td>
<td><strong>EMs (detected) and PMs (not detected)</strong>&lt;br&gt; PMs had low concentrations of M6G and NM</td>
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<td>Morphine and morphine metabolites</td>
<td><strong>EMs (detected) and PMs (not detected)</strong>&lt;br&gt; PMs had low concentrations of M6G and NM</td>
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<td>Codeine metabolic clearance by O-demethylation</td>
<td><strong>EMs (detected) and PMs (not detected)</strong>&lt;br&gt; PMs had low concentrations of M6G and NM</td>
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<tr>
<td>Healthy volunteers (Sweden)</td>
<td>28</td>
<td>Morphin and morphine metabolites</td>
<td><strong>EMs or M6G were detected in all EMs but only detected at a low level in one PM subject</strong>&lt;br&gt; Codeine significantly reduced peak pain and discomfort-median peak change of 5.5 mm for peak pain and 10.5 mm for discomfort in EMs&lt;br&gt; No effect of codeine in PMs&lt;br&gt; No significant difference between codeine and placebo in PMs&lt;br&gt; More pronounced adverse effects of codeine as compared to placebo in EMs (Morphine, M6G, M3G and NM)</td>
<td>82)</td>
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<td></td>
<td></td>
<td>Pain tests <em>(Cold pressor test)</em></td>
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<td>Side-effects</td>
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<td></td>
<td>Pharmacokinetic parameters of morphine</td>
<td><strong>EMs &gt; PMs</strong>&lt;br&gt; Codeine significantly prolonged transit time in EMs&lt;br&gt; No significant difference between codeine and placebo in PMs&lt;br&gt; More pronounced adverse effects of codeine as compared to placebo in EMs (Morphine, M6G, M3G and NM)</td>
<td>85)</td>
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<tr>
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<td>O-Deacetyl transit time</td>
<td></td>
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<tr>
<td>Male healthy volunteers (Germany)</td>
<td>10</td>
<td>Amount of morphine</td>
<td><strong>EMs &gt; PMs</strong>&lt;br&gt; Codeine significantly prolonged transit time in EMs&lt;br&gt; No significant difference between codeine and placebo in PMs&lt;br&gt; More pronounced adverse effects of codeine as compared to placebo in EMs (Morphine, M6G, M3G and NM)</td>
<td>82)</td>
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<tr>
<td></td>
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<td>Percentage of the codeine dose converted to morphine and its metabolites</td>
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<td>Pain tolerance <em>(Cold pressor test)</em></td>
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<td></td>
<td></td>
<td>Frequency and intensity of adverse events</td>
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<tr>
<td>Healthy volunteers (Germany)</td>
<td>18</td>
<td>AUCs of morphine</td>
<td><strong>EMs &gt; EMs</strong>&lt;br&gt; EMs &gt; PMs&lt;br&gt; (Codeine + codeine-6-glucuronide divided by the sum of morphine + its glucuronides metabolites)&lt;br&gt; PMs &gt; EMs and UMs&lt;br&gt; UMs &lt; EMs&lt;br&gt; No significant difference between phenotypes&lt;br&gt; No significant differences between phenotypes</td>
<td>86)</td>
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<td></td>
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<td>Metabolic ratios</td>
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<td></td>
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<td>Pupil diameter</td>
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<td></td>
<td>Side-effects</td>
<td></td>
<td></td>
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<tr>
<td>Caucasian male healthy volunteers (Germany)</td>
<td>26</td>
<td>Total pain</td>
<td><strong>EMs &gt; PMs</strong>&lt;br&gt; Codeine significantly prolonged transit time in EMs&lt;br&gt; No significant difference between codeine and placebo in PMs&lt;br&gt; More pronounced adverse effects of codeine as compared to placebo in EMs (Morphine, M6G, M3G and NM)</td>
<td>82)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CYP2D6 genotype showed no correlation with area under the curve of pain</td>
<td></td>
<td>31)</td>
</tr>
<tr>
<td>Post-partum pain post-cesarean section</td>
<td>45</td>
<td>Morphine concentration</td>
<td><strong>Group I (n = 30) had measurable morphine concentration</strong>&lt;br&gt; <strong>Group II (n = 24) had unmeasurable morphine concentrations</strong> (Carrier of *17, *29, or *41 allele)&lt;br&gt; <strong>Group III (n = 9, 30.0%) &lt; Group II (n = 11, 46.0%) (p = 0.23)</strong>&lt;br&gt; <strong>Group I (n = 1, 3.0%) &lt; Group II (n = 5, 21.0%) (p = 0.07)</strong>&lt;br&gt; No significant differences between metabolic status&lt;br&gt; More hospital admissions in patients with no measurable morphine concentrations</td>
<td>93)</td>
</tr>
<tr>
<td>(Mixed ethnicity–Canada)</td>
<td></td>
<td>Allele and genotype frequency</td>
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<td>Emergency room visits</td>
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<td></td>
<td>Hospital admissions</td>
<td></td>
<td></td>
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<tr>
<td>Blacks (United States of America)</td>
<td>54</td>
<td>Morphine concentration</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Allele and genotype frequency</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Emergency room visits</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Hospital admissions</td>
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<table>
<thead>
<tr>
<th>Study population</th>
<th>CYP2D6 polymorphism, N</th>
<th>Variable</th>
<th>Result</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children with sickle cell pain crisis (United State of America)</td>
<td>73</td>
<td>Pain crisis</td>
<td>An increase in reduced functioning CYP2D6 allele is associated with failing codeine therapy for a pain crisis while taking hydroxyurea</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Reduced-functioning allele = 42</td>
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<tr>
<td></td>
<td>Duplication = 10</td>
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<tr>
<td></td>
<td>Deletion = 15</td>
<td></td>
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</tr>
<tr>
<td>Children after adenotonsillectomy (Mixed ethnicity-United Kingdom)</td>
<td>96</td>
<td>Morphine and morphine metabolites</td>
<td>Significant differences in plasma morphine between phenotypes</td>
<td>92</td>
</tr>
<tr>
<td></td>
<td>PM = 4</td>
<td>Pain score</td>
<td>Plasma morphine and metabolite concentrations were very low or absent in greater proportions of those in the low-activity groups</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IM/PM = 17</td>
<td>Need for rescue analgesia</td>
<td>No significant differences between phenotypes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IM = 29</td>
<td>Side-effects</td>
<td>No significant differences between phenotypes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>EM = 45</td>
<td></td>
<td>No significant differences between phenotypes</td>
<td></td>
</tr>
<tr>
<td>Patients with post-operative pain (Denmark)</td>
<td>81</td>
<td>Morphine and morphine metabolites</td>
<td>In PMs, morphine and M6G were below the limit of detection</td>
<td>91</td>
</tr>
<tr>
<td></td>
<td>PM = 8</td>
<td>Pain relief</td>
<td>The sum of differences between pre- and post-operative pain ratings did not differ between phenotypes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>EM = 66</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>ND = 7</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>(phenotyped with dextromethorphan)</td>
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<tr>
<td>Women after hysterectomy (Sweden)</td>
<td>11</td>
<td>Pain relief</td>
<td>Two patients did not experience any effect of codeine, one of whom was a PM</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>PM = 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>EM = 10</td>
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<tr>
<td></td>
<td>(phenotyped with dextromethorphan)</td>
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N, number of subject; PM, poor metabolizer; IM, intermediate metabolizer; EM, extensive metabolizer; UM, ultra-rapid metabolizer; AUCs, areas under the plasma concentration vs. time curves; M6G, morphine-6-glucuronide; M3G, morphine-3-glucuronide; NM, normorphine; ND, no data.

Sulfapyridine method, assuming that no effects are observed in PMs because negligible amounts of morphine are formed. In EMs, oro-caecal transit time was significantly prolonged compared to a placebo, whereas no significant difference occurred in PMs. They concluded that because the oro-caecal transit time prolongation after codeine administration was observed only in EMs, the effect of codeine on gastrointestinal motility, like the analgesia, is mediated by its metabolite morphine.

Correspondingly, in all the studies morphine and morphine metabolites were detectable only in plasma from EMs and no or only low levels could be detected in PMs. It is thus indicated that the opioid related side-effects of codeine are mainly related to the metabolically formed morphine and/or morphine metabolites like the analgesic effects. However, another study found that five (42.0%) of the 12 EMs and two (66.0%) of the PMs had at least one adverse effect when combining all side-effects (p = 0.041). The association between CYP2D6 PM phenotype and opioid related side-effects of codeine were not shown in subsequent studies.

The association between CYP2D6 PM phenotype and opioid related side-effects of codeine were not shown in subsequent studies. Kircheiner et al. investigated the codeine effect on mu-type opioid receptors by measurement of pupil size. There was no significant difference in the pupil diameter between EMs and PMs, even though the pupil diameter in PMs was larger than in EMs.

Hasselstrom et al. found no significant difference in inhibition of gastrointestinal transit between the CYP2D6 phenotypes when they administered codeine to EMs (debrisoquine metabolic ratio (MR) of less than 1) and PMs (MR >12.6). They concluded that the prolongation of gastrointestinal transit caused by the drug does not depend on the formation of O-demethylated active metabolite morphine, M6G or NM. Therefore, codeine or its N-demethylated or glucuronidated metabolites may be the active moieties for the important gastrointestinal effects.

Eckhardt et al. tested the hypothesis that the adverse effects of codeine are mediated by the parent drug and not its metabolite morphine. There was no difference between the PMs and EMs in the frequency and intensity of the adverse events. Thus, using a high dose of codeine (170 mg) in this study, the adverse events seem to occur independently from morphine formation (since only traces of morphine in plasma could be detected in PMs and higher amounts of morphine were detected in EMs), as they occur both in EMs and PMs. Therefore, the adverse events seem to be related to codeine itself. The authors suggested that PMs may show no analgesic effects from codeine doses up to 170 mg (since they found that PMs did not show an analgesic effect compared to a placebo) but may suffer side-effects caused by codeine itself.

In addition, inhibition of CYP2D6 by numerous drugs will also result in diminished or even absent pharmacodynamic effects of codeine in EMs. Studies have been done to determine whether the inhibition of codeine’s metabolism by quinidine (environmental alteration of the phenotypic expression) produces phenotypically dependent pharmacokinetics and pharmacodynamic changes in phenotyped healthy volunteers. Desmeules et al. found that morphine production was diminished in Ems, resulting in a plasma morphine profile similar to that in the PMs of genetic origin. They also observed no detectable effect of codeine in the subjective or objective pain threshold (p < 0.001) responses to selective transcutaneous nerve stimulation. In another study, morphine and morphine metabolites were not detectable in the plasma of EMs and the O-demethylation clearance was significantly reduced from 162.7 to 17.0 mL/min after coadministration of quinidine. The diminished production of morphine in the EMs was associated with significantly reduced respiratory, psychomotor and pupillary effects (p < 0.01). Thus, the administration of quinidine or other drugs which inhibit CYP2D6 will abolish codeine’s analgesia and respiratory depressant effects.

The clinical importance of these finding is that EMs may suffer disastrous side-effects if the quinidine or other CYP2D6 inhibitor is stopped and subsequently the dose of codeine is increased in clinical situations such as in a patient non-responding to codeine,
because this would result in inappropriately high codeine doses and potentially lethal respiratory depression. Thus, phenotyping for CYP2D6 and the avoidance of CYP2D6 inhibitors is justified in patients with chronic pain treatment before initiating long-term therapy with analgesics whose \textit{in vivo} activation is dependent on CYP2D6 activity.

In contrast to previous investigations focusing on experimental pain models in healthy volunteers,\textsuperscript{33,34,83} a clinical setting of acute pain patients recovering from surgery was used in the study by Persson \textit{et al.}\textsuperscript{90} in attempt to define the kinetics and efficacy of codeine in post-operative pain relief. Patient-controlled analgesia (PCA) was used to administer codeine when the patient required pain relief for the first time after surgery. Pain was assessed before the start of PCA at 1, 2 and 4 h and then every 4 h thereafter. Two patients did not experience any effect of codeine, one of whom was an EM who had severe hip damage which required more potent analgesia. Another patient was a PM and hence a low rate of morphine formation might be expected to have contributed to therapeutic failure. Therefore, the differences in codeine metabolism between EMs and PMs have an impact on PCA. Thus, the data obtained in the single PM emphasizes the need for further studies of the role of CYP2D6 and morphine generated from codeine on the effect of codeine when used to treat post-operative pain.

In contrast, a larger study of the post-operative effect of codeine did not reveal any differences between PMs and EMs in pain rating.\textsuperscript{91} Poulsen \textit{et al.}\textsuperscript{91} determined the serum concentration of codeine and its metabolites and the sum of differences between pre- and post-operative pain ratings after a single oral dose of 100 mg codeine. In line with the studies in healthy volunteers,\textsuperscript{82,85,87,89} they found that in PMs morphine and its metabolites cannot be detected after codeine intake. But, they also found that in some EMs, a substantial number of patients had very low levels of morphine and its metabolites. The decreased efficacy of codeine in these patients may be related to the low concentrations of these active substances. However, there was no significant difference between the two phenotypes in the pain relief after oral codeine in post-operative patients, probably due to the small number of PMs.

Later, Williams \textit{et al.}\textsuperscript{92} investigated genotype, phenotype and morphine production from codeine in children undergoing adenotonsillectomy. They examined the efficacy and side-effects of codeine as part of a post-operative analgesic regimen. In this randomized, double-blind study, children were given intramuscular codeine or morphine in combination with diclofenac per rectum. In line with the previous studies in post-operative patients given a single oral dose of codeine,\textsuperscript{93} they found no morphine or metabolites (M6G and morphine-3-glucuronide (M3G)) measurable in the two PMs. Some heterozygous patients with declining metabolic capacity also had no morphine or metabolites (M6G and M3G) measurable in their plasma. This study showed a significant relationship between CYP2D6 phenotypes and plasma morphine. However, no relationship could be found between CYP2D6 phenotypes and analgesia. PMs did not differ significantly from other phenotypes in the pain score or the need for rescue analgesia despite a demonstrated lack of plasma morphine. The side-effects of codeine such as post-operative nausea and vomiting were also evenly distributed among the phenotypes.

In line with the two previous studies in patients with acute pain,\textsuperscript{91,92} VanderVaart \textit{et al.}\textsuperscript{31} in a pilot study also found no correlation between \textit{CYP2D6} genotype and total pain when codeine was used on an as-needed basis. However, the potential effects of \textit{CYP2D6} genotype were illustrated in the UMs and PMs. The two PMs reported no analgesia as a result of taking codeine, whereas two of the three UMs reported immediate pain relief from codeine but stopped taking it due to dizziness and constipation. They concluded that the extreme \textit{CYP2D6} genotypes (PMs and UMs) seemed to predict pain response and adverse events. However, larger sample sizes are needed to correlate the range of genotypes with pain response. In this study, the measurement of enzyme activity and morphine concentration were not done. Therefore, the relationship between \textit{CYP2D6} genotypes and plasma morphine could not be analyzed.

The link between the \textit{CYP2D6} phenotypes and a clinically relevant decrease in pain relief after codeine use also has been examined in other pain settings. Children with sickle cell disease presenting to an emergency department with a pain crisis unresponsive to codeine were evaluated by Brousseau \textit{et al.}\textsuperscript{30} The proportion of children having at least one reduced-functioning allele, \textit{CYP2D6}\textsuperscript{1.5}, \textsuperscript{9}, \textsuperscript{10}, \textsuperscript{11}, \textsuperscript{17}, \textsuperscript{18} and \textsuperscript{40} and \textit{CYP2D6} activity score were measured. The activity score, based on extensive genotypetype/phenotype comparisons was used to approximate the phenotype for a given genotype in an individual. It was assumed that high metabolizers more readily convert codeine to its active form, resulting in improved pain control, while children with activity scores ≤1.5 have decreased activation of codeine and thus decreased pain control. The result confirmed the hypothesis that children taking hydroxyurea undergoing ineffective pain treatment of sickle cell crisis with codeine were more likely to have a reduced-functioning \textit{CYP2D6} allele and reduced \textit{CYP2D6} activity. They concluded that children taking hydroxyurea who continue to present to the emergency department for sickle cell pain crisis after failing oral codeine warrant \textit{CYP2D6} genotyping. Alternatively, these children could be given a non-\textit{CYP2D6}-dependent analgesic for pain. However, no measurement of enzyme activity or morphine concentration was done in this study. Therefore, the relationship between \textit{CYP2D6} phenotypes and plasma morphine could not be analyzed.

In contrast, Shord \textit{et al.}\textsuperscript{93} in their prospective, open-label study showed that Blacks with sickle cell disease without measurable plasma morphine levels after a single dose of codeine were not more likely to be a carrier of a single variant allele commonly associated with reduced \textit{CYP2D6} metabolic capacity. However, homozygosity for a variant \textit{CYP2D6} allele may result in reduced metabolic capacity. Three variant alleles (\textit{CYP2D6}\textsuperscript{1.7}, \textsuperscript{41} and \textsuperscript{41}) were detected in this study. They proposed that Blacks with sickle cell disease carrying \textit{CYP2D6}\textsuperscript{1.7} or \textsuperscript{41} allele will report minimal or no analgesia with codeine and that these patients may be more likely to seek medical care with the need for other opioids for acute pain management. They found that subjects without measurable morphine concentrations were more likely to be admitted to the hospital for an acute pain crisis, but emergency room visits did not differ based on metabolic status.

At the opposite side of the \textit{CYP2D6} PM phenotype, the UM phenotype is assumed to have a higher concentration of active metabolites of codeine and may experience exaggerated and even potentially dangerous opioidergic effects. Individuals phenotyped as \textit{CYP2D6} UMs have been reported to develop up to 45-fold higher concentrations of codeine O-demethylated metabolites than PMs after 25 mg codeine in 156 healthy Caucasians.\textsuperscript{94} In this study, only urinary codeine and its seven metabolites were detected and blood level measurement was not done. The reported \textit{CYP2D6}
phenotypes were based on debrisoquine metabolic ratios (MR) (24 UMs, MR < 0.11; 114 EMs, MR < 12.6 and 18 PMs MR > 12.6).

Kirchheiner et al. investigated the differences in codeine metabolite pharmacokinetics between EMs and UMs according to CYP2D6 genotype. They administered a single dose of 30 mg codeine and pharmacokinetics was measured over 24 h after drug intake. Codeine and its metabolites were analyzed in plasma and urine. In line with the previous finding of higher concentrations of O-demethylated metabolites in UMs than PMs, this study found that the areas under the plasma concentration vs. time curves (AUCs) of morphine was increased by 45.0% in UMs compared to EMs (16 vs. 11 µg.h/L) (p = 0.02). They demonstrated that CYP2D6 genotypes predicting ultra-rapid metabolism resulted in about 50.0% higher plasma concentrations of morphine and its glucuronides compared with the EMs. In term of opioidergic effects, ten of the 11 UMs felt sedation (91.0%) compared to six (50.0%) of the 12 EMs (p = 0.03). When combining all side-effects, all of the UMs and five (42.0%) of the 12 EMs had at least one side-effect. However, there was no significant effect of CYP2D6 genotypes on pupil diameter. No severe adverse effects were seen in the UMs in this study, most likely because a low dose of only 30 mg was used for safety reasons. They concluded that ultra-rapid codeine metabolism caused by a CYP2D6 gene duplication resulted in a 1.5-fold higher morphine exposure compared to that of EMs. This difference is only moderate but the risk for opioid intoxication might be increased in UMs if additional factors such as reduction in renal function or further inhibition of other enzyme systems occur. Therefore, it would help if physicians administering codeine are aware of the impact of a CYP2D6 duplication genotype in their patients.

Several case reports have also commented on the clinical impact of codeine in CYP2D6 UM largely because of the large amount of morphine formed by these patients. Dalen et al. reported an UM woman (phenotyped with debrisoquine, duplication of CYP2D6*2), Caucasian, aged 33 years from Sweden who received 60 mg codeine prophylactically to avoid pain following a tooth extraction. Within 30 min, the patient experienced euphoria, dizziness, and visual disturbance. Simultaneously, she experienced very severe epigastric pain. The euphoria and pain lasted for approximately 3 to 4 h and then vanished. A re-challenge with codeine 30 mg resulted in the same symptoms, although they were less pronounced.

Gasche et al. described an UM male (three or more functional alleles, MR dextromethorphan less than 0.0005), aged 62 years from Switzerland with renal failure taking codeine 25 mg three days a time to relieve a cough. The patient was prescribed concomitantly with CYP3A4 inhibitors (clarithromycin and voriconazole) for bilateral pneumonia. On hospital day 4, the patient’s level of consciousness rapidly deteriorated, and he became unresponsive. Intravenous administration of naloxone resulted in a dramatic improvement in the patient’s level of consciousness. Morphine plasma concentration was 80 µg/L (expected range, 1 to 4 µg/L). They attributed the toxicity to this genotype, in combination with inhibition of CYP3A4 activity by other medications and a transient reduction in renal function. This case supports the potential usefulness of the determination of genotype and phenotype in elucidating serious adverse events and in preventing subsequent inappropriate selection or doses of drugs.

Another case report highlighted the risks of codeine use in a breast-fed male infant, aged 13 days from Canada in association with the UM phenotype (mother heterozygous for a CYP2D6*2A allele with CYP2D6*2 × 2 gene duplication). After delivery, his mother was prescribed codeine 120 mg/day and the dose was reduced by the mother to 60 mg/day on day 2 owing to somnolence and constipation. The baby showed intermittent periods of difficulty in breast-feeding and lethargy starting on day 7. On day 11 the baby had regained his birthweight. On day 12, however, he had grey skin and his milk intake had fallen. He was found dead on day 13. The post-mortem blood concentration of morphine was 70 ng/mL (normal range: 0 to 2.2 ng/mL). Death of this newborn was attributed to opioid overdose. This case shows that polymorphism of CYP2D6 can be life threatening for some breast-fed babies and codeine cannot be considered as a safe drug for all babies during breast-feeding.

Another case report of a boy, aged two years from Canada, who died from a codeine overdose after adenotonsillectomy highlighted the significant increase of risk of respiratory depression in UM (functional duplication of CYP2D6 allele). In this case, the prescribed and administered dose of codeine (10 to 12.5 mg every 4 to 6 h) was within the recommended range of 1 to 3 mg per kilogram of body weight per day. It appeared that the concentration of 32 ng/mL of morphine at autopsy exceeded therapeutic levels and may have contributed to respiratory depression and death. This case showed that codeine cannot be considered a safe outpatient analgesic for young children after adenotonsillectomy.

Another previously healthy boy aged 29 months of North African descent from the United States of America experienced apnea resulting in brain injury following a dose of acetaminophen and codeine 2 days after an uneventful anesthesia for a tonsillectomy. The authors agreed with the concept that research needs to be organized to determine the role, if any, of codeine conclusively in the attempt to alleviate pain.

In a case-controlled study, two mothers whose infants exhibited severe neonatal toxicity were identified as carrying the combined genotypes of a CYP2D6 UM and UGT2B7*2/*2. Therefore, this study suggested a possible additional role of the polymorphic UDP glucuronosyltransferase 2 family, polypeptide B7 (UGT2B7), which catalyzes the glucuronidation of morphine to M6G and M3G. This case showed that breast-fed infants of mothers who are CYP2D6 UMs combined with the UGT2B7*2/*2 are at increased risk of potentially life-threatening CNS depression.

The reported case of death of a breast-fed 13-day-old neonate following a morphine overdose because his mother was taking codeine after childbirth led to a U.S. Food and Drug Administration (FDA) warning on the prescription of codeine to nursing mothers. Besides that, previous findings in the literature suggested the potential usefulness of the determination of genotype and phenotype in elucidating serious adverse events and in preventing subsequent inappropriate selection or doses of codeine. A new guideline regarding the use of pharmacogenomic tests in dosing for codeine has been published by the Clinical Pharmacogenetics Implementation Consortium (CPIC). This guideline is available at http://www.pharmgkb.org/index.jsp.

**Tramadol**

Tramadol is an analgesic drug, a synthetic analogue of codeine, acting on mu-type opioid receptors. CYP2D6 catalyses tramadol O-demethylation to O-desmethytramadol (M1) in human liver microsomes, which has a major impact on the analgesic effect and other pharmacodynamics effects. Tramadol is N-demeth-
Table 3. Association studies of CYP2D6 polymorphisms with pharmacokinetics and pharmacodynamics of tramadol

<table>
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<th>Study population</th>
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<td>No significant differences between genotypes</td>
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N, number of subject; PM, poor metabolizer; IM, intermediate metabolizer; EM, extensive metabolizer; UM, ultra-rapid metabolizer; hetEM, heterozygous extensive metabolizer; homEM, homozygous extensive metabolizer; M1, O-desmethyltramadol; (+)-M1, (+)-O-desmethyltramadol; PCA, patient controlled analgesia; AUC, area under the plasma concentration-time curve; Cmax, maximum plasma concentration; AUD, area under the time-effect concentration profile; Emax, maximum papillary constriction effect.

Significant correlation between sparteine oxidation and tramadol O-demethylation in EMs. They concluded that polymorphic CYP2D6 is involved to a large extent in tramadol metabolism.

Later, Enggaard et al. [102] found that (+)-O-desmethyltramadol (+)-M1 concentrations were below the limit of determination in all PMs, whereas the active metabolite could be detected in the serum samples from all EMs except one. The concentrations of (+)-M1 were significantly larger in the EMs than in the PMs at all measurements (p < 0.01 at 15 min and p < 0.001 at 30, 60, and 90 min).

There were substantially higher mean area under the plasma concentration-time curve (AUC) and maximum plasma concentration (Cmax) values for tramadol in PMs compared to both EMs.

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groups. In the case of M1, PMs had three to four times lower AUC and $C_{\text{max}}$ values compared to both EM groups.

The tramadol pharmacokinetics in the CYP2D6 UM phenotype was studied by Kirchheiner et al. In the UMs, the maximum plasma concentrations ($C_{\text{max}}$) of the active metabolite (+)-R,R,O-desmethyltramadol were significantly higher than in the EM volunteers (mean difference of 14 ng/mL, $p = 0.005$).

The impact of the other CYP2D6 genotypes and phenotypes on tramadol pharmacokinetics among acute pain patients were reported by Gan et al. In an earlier study, Gan et al. investigated the influence of the CYP2D6*10 allele on the disposition of IV bolus tramadol (100 mg) in Malaysian patients (28 Malays and two Chinese). They found that patients who were homozygous for CYP2D6*10 had a significantly longer mean half-life of tramadol than patients of the normal or the heterozygous group ($p = 0.046$). They also found that the CYP2D6*10 allele particularly was associated with higher serum levels of tramadol compared with the CYP2D6*1 allele. When larger numbers of Malaysian patients were recruited ($n = 138$), Gan et al. found that UMs and EMs had 2.6- and 1.3-times faster total clearance, respectively, than the IMs. The mean total clearance was 16, 18, 23, and 42 L/h while mean half-lives were 7.1, 6.8, 5.6, and 3.8 h among the IMs (carrying one CYP2D6 allele associated with diminished CYP2D6 activity ($*9, *10, *17$) and/or one non-functional CYP2D6 allele ($*3, *4, or *5$), EM1s (homozygous wild-type), EM2s (carrying only the wild-type), and UMs, respectively. They concluded that CYP2D6 activity may play a main role in determining tramadol pharmacokinetics.

In a randomized, double-blind, placebo-controlled trial with a single IV bolus of tramadol (100 mg) against a placebo, Enggaard et al. assessed the analgesic effect of tramadol on different types of experimental pain in relation to CYP2D6 phenotype. Repetitive electrical sural nerve stimulation (RES) and a cold pressor test were performed before and 15, 30, 60, and 90 min after medication. The suggestion that the analgesic effect of tramadol depends on the genetic polymorphic O-demethylation of tramadol to (+)-M1 was supported, since tramadol only reduced discomfort during the cold pressor test significantly in EMs ($p < 0.002$), whereas no effect was observed in the PMs. This study also indicated that the monoaminergic mechanisms of the parent compound contribute to the action, as there was some effect in the PMs. In the PMs tramadol produced a significant increase in the pain tolerance thresholds ($p = 0.04$) to sural nerve stimulation, whereas no detectable effect was observed in the EMs. They concluded that the biotransformation of tramadol to the metabolite (+)-M1 via CYP2D6 has a major impact on the analgesic effect of tramadol, as (+)-M1 appears to create the opioid effect of tramadol. However, the monoaminergic effect of the parent compound itself seems to have an analgesic effect.

Slanar et al. determined the opioid effects measured by pupillary response to a single slow-released tablet of 100 mg tramadol in relation to the disposition of tramadol and M1 in plasma among CYP2D6 genotyped subjects. They found different patterns of miotic response between PMs and EMs. The area under the time-effect concentration profile (AUD) and maximum papillary constriction effect ($E_{\text{max}}$) were significantly greater in homozygous EMs than PMs.

Lier, Kirchheiner et al. detected a clear trend toward lower opioid effects with decreasing CYP2D6 activity when comparing UMs, EMs, and PMs. They found that PMs had less miosis. However, there was no increase in pain threshold or in pain tolerance in these three individuals. Inversely, pharmacodynamic assessments demonstrated an increased pain threshold and pain tolerance in UMs compared with EMs. They also observed a trend toward stronger miosis in the UMs compared with the EMs.

Three studies reported the impact of the CYP2D6 genotypes and phenotypes on tramadol analgesia among acute pain patients. Stamer et al. investigated whether the CYP2D6 genotype influenced the post-operative analgesia of tramadol (via IV bolus (100 mg), PCA (combination of tramadol 20 mg/mL, dipyrone 200 mg/mL and metoclopramide 0.4 mg/mL and continuous infusion). They compared the pain scores, analgesic consumption and need for rescue medication between heterozygous EMs (patients with at least one functional allele) and PMs. The hypothesis of reduced analgesic efficacy of tramadol in PM was confirmed when they found that a well characterized group of PMs differed significantly in their response compared with the large group of patients carrying at least one wild-type allele. The percentage of non-responders was significantly higher in the PMs (46.7%) than the EMs (21.6%). PMs consumed more tramadol than EMs. The tramadol loading dose was 33.0% lower in EMs than PMs (108.3 vs. 144.2 mg). Since the study protocol allowed the application of rescue medication in case of insufficient pain management, pain scores under rest and exercise did not differ among the genotypes. PMs consumed more additional rescue medication than EMs. A higher percentage of PMs than EMs received rescue medication in the recovery room and during the PCA period. They concluded that genetic polymorphisms of CYP2D6 (*3, *4, *5, and *6) do have an impact on post-operative analgesia and should be considered if patients do not adequately respond to tramadol.

The effect of the CYP2D6*10 C188T polymorphism on post-operative tramadol analgesia was investigated in a prospective study by Wang et al. Each patient received a loading dose of 100 mg IV bolus tramadol. Patients could self-administer doses of the drug combination (10 mg/mL tramadol plus 0.3 mg/mL metoclopramide) via PCA for the further 48-h study period. Patients were categorized into three groups according to the CYP2D6 genotype: patients without CYP2D6*10 (group I), patients heterozygous for CYP2D6*10 (group II), and patients homozygous for CYP2D6*10 (group III). There was no difference in the total consumption of tramadol among the three groups at 2 h. The consumption of tramadol in group III was significantly higher than that in groups I or II at 4, 24, and 48 h, while it did not differ between groups I and II. Since the study protocol allowed the application of tramadol via PCA and rescue medication tramadol was given if analgesia was insufficient, pain scores did not differ among genotypes. The number of patients who were unsatisfied with analgesia in group III was higher than that in group I and II (group I, n = 2, group II, n = 3 and group III, n = 6). However, there was no significant difference in the satisfaction among the genotype groups. This study showed for the first time that the presence of a genotype coding for the low active CYP2D6 protein CYP2D6*10 alters the response to tramadol treatment. Therefore, this could have major implications in the interindividual treatment of post-operative pain.

Later, Slanar et al. evaluated tramadol efficacy in relation to CYP2D6 and MDR1 polymorphisms. Tramadol was given on demand intramuscularly at a dosage of 100 mg for one application or orally 50 mg in immediate release formulation. Pain intensity
was assessed using a visual analogue scale (VAS) at 2 and 24 h after the surgery. In addition, the patients’ verbal description of pain using the standardized short version of the McGill Pain Questionnaire was evaluated. Patients carrying two inactive alleles were classified as PMs, patients with one active and one variant allele were classified as heterozygous extensive metabolizers (hetEMs) and subjects with no variant and two active alleles were assigned to the homozgyous extensive metabolizer (homEM) phenotype. Subjects with more than two active alleles formed a group of UMs. They found that the mean pain difference was lowest in the UM and highest in the PM. The pain difference varied significantly among the CYP2D6 subgroups with significant differences between homEM vs. hetEM, homEM vs. PM, and UM vs. PM subgroups. There were no significant differences in the drug consumption, need for rescue analgesic medication or verbal description of pain among the CYP2D6 genotype subgroups. They concluded that CYP2D6 plays a significant role in tramadol analgesic efficacy.

In term of adverse effects, UMs were more sensitive to tramadol than EMs. Kirchheiner et al. demonstrated that UM volunteers experienced quicker analgesic effects but were prone to higher mu-opioid-related toxicity after tramadol in an experimental pain setting using a cold pressure test when they studied 11 carriers of a CYP2D6 duplication allele (UMs) and compared them with 11 carriers of two active CYP2D6 (EMs). Pharmacokinetics and pharmacodynamics effects (pain threshold and pain tolerance, miosis and adverse events) were monitored after a single dose of 100 mg racemic tramadol, rapid release formulation. They observed differences in tramadol adverse effects with a higher frequency of nausea (50.0 vs. 9.0%) in the UMs compared with the EMs.

Several case reports have commented that the exaggerated and even potentially dangerous opioidergic effects experienced by CYP2D6 UMs may be related to the large amount of active metabolite (+)-M1 formed by these patients. A UM aged 66 years old with renal impairment developed opioid-related respiratory depression after surgery for recurring renal carcinoma. He received tramadol via PCA. Complete recovery occurred after naloxone administration, thus confirming opioid intoxication. The authors suggested that genetic CYP2D6 variation should be a future diagnostic target whenever administration of tramadol or codeine is anticipated.

On the other hand, Gan et al. suggested that the slower metabolizers of tramadol tend to experience more adverse effects of the drug. Their results showed that IM, who are the slowest metabolizers of tramadol within their study population were found to have a statistically higher incidence of adverse drug reactions (dizziness, headache, nausea, sweating and dry mouth) when compared with the groups that metabolize tramadol faster (UMs and EMs).

Other studies found no difference in term of adverse events such as nausea and vomiting between patients with the CYP2D6 UM phenotype, PM phenotype or reduced CYP2D6 activity and EMs.

Conclusion

There were few studies that investigated the association between pain sensitivity and CYP2D6 polymorphisms and the result remains controversial. Further studies are necessary to evaluate the results of these association studies.
Acknowledgments: We thank Prof. Howard McNulty of the Institute of Pharmacy and Bio-medical Sciences University of Strathclyde for English language editing and proofreading of this article.

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