Assessment of Effects of Chronic Hydrogen Sulfide Poisoning on Cytochrome P450 Isoforms Activity of Rats by Cocktail Approach

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Hydrogen sulfide (H2S) is one of the neurotoxic gases with suffocating and irritating. Its main target organs of toxic effects are the central nervous system and respiratory system. Cocktail method was used to evaluate the influence of chronic hydrogen sulfide poisoning on the activities of cytochrome P450 (CYP450) isoforms CYP1A2, CYP2C9, CYP2B6 and CYP2D6, which were reflected by the changes of pharmacokinetic parameters of 4 specific probe drugs phenacetin, tolbutamide bupropion and metoprolol, respectively. The experimental rats were randomly divided into two groups, control group and chronic hydrogen sulfide poisoning group. The chronic hydrogen sulfide poisoning group rats were inhaled 20 ppm for 1 h twice a day for 40 d. The mixture of 4 probes was given to rats through sublingual veins and the blood samples were obtained at a series of time-points through the caudal vein. The concentrations of probe drugs in rat plasma were measured by liquid chromatography-mass spectrometry (LC-MS). In the experiment for chronic hydrogen sulfide poisoning and control group, there was a statistically significant difference in the area under the plasma concentration–time curve from zero to infinity (AUC0–∞), plasma clearance (CL) and maximum plasma concentration (Cmax) for phenacetin and bupropion, while there was no statistical pharmacokinetics difference for tolbutamide and metoprolol. Chronic hydrogen sulfide poisoning could induce the activity of CYP1A2 and CYP2B6 of rats.

Key words cytochrome P450; chronic hydrogen sulfide poisoning; cocktail; LC-MS

Hydrogen sulfide (H2S) is one of the neurotoxic gases with suffocating and irritating. Its main target organs of toxic effects are the central nervous system and respiratory system. It can also be associated with heart and multiple organs damages. There was some study investigated the most sensitive tissues of the toxic effects were the brain and the mucous membranes which were exposed to hydrogen sulfide.1,2) Hydrogen sulfide is often found in the waste gases and water emissions, there are 70 kinds of occupational exposures. It has been reported that the number of spontaneous abortion rises in the area when H2S content >0.003 ppm. Hydrogen sulfide poisoning is dose-related. When exposure concentration of hydrogen sulfide is more than 494 ppm, it will produce dysphoria, delirium, twitch, incontinence and falling into a coma state quickly. It can cause poisoning pneumonia, pulmonary edema or cerebral edema simultaneously; and may even appear obvious myocardial and multiple organs damages. When exposure concentration of hydrogen sulfide is more than 71 ppm, it will produce “shock-like” poisoning which can occur with the onset of coma, twitch, breathing and heartbeat rapid stoppings one after another in few seconds after hydrogen sulfide poisoning.

Cytochrome P450 (CYP450) is a super-gene family; it can code 500 kinds of enzymes and mainly be found in the liver and small bowel in vivo. CYP450 enzymes exist many isozymes, it can be divided into a number of genes/sub-genes families, the enzymes of the same family own similar functions.3,4) CYP450 enzymes belongs to the hemoglobin enzymes, which is the most important family in the microsomal mixed function oxidases, it distributed in variety of organs and tissues.5) There are 39 active CYP enzymes which are found in vivo, and most of them are involved in the metabolism of endogenous substances.5) When a certain kind of enzyme activity change, the corresponding metabolism of substrate drugs will also change. To a certain extent, it will cause drug interactions and adverse drug reactions. That is the reason the activity of hepatic drug metabolizing enzyme subtypes have been received more and more attention.

In recent years, we mainly evaluate the influence of drugs or other factors on the CYP450 enzymes through the probe drugs. Traditionally, we use only one probe drug one time, it can only reflect one or a part of the CYP450 enzyme activity. This method is time-consuming, laborious and individual differences. Therefore, the researchers are trying to use a variety of probe drugs at the same time that enabled simultaneous reflection of multiple isoenzyme activities in a single run. The “Cocktail” probe drugs approach can reflect a plurality of information of the CYP450 enzymes at the same time, greatly shorten and reduced the experimental time and cost.7,8)

At present, the study of hydrogen sulfide toxicology is mainly focus on the central nervous system and cardiovascular system.9–15) To our knowledge, there are few reports about the hepatic toxicity of hydrogen sulfide. In this paper, “Cocktail” probe drugs approach is used to evaluate the induction or inhibition effects of chronic hydrogen sulfide poisoning on the activities of rats cytochrome P450 isoforms such as CYP1A2, CYP2C9, CYP2B6 and CYP2D6, which are reflected by the changes of pharmacokinetic parameters from 4 specific probe drugs phenacetin, tolbutamide, bupropion and metoprolol, then provide a guidance for rational clinical administration.

The authors declare no conflict of interest.

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after the inhalation of H₂S.

MATERIALS AND METHODS

Chemicals and Reagents Phenacetin, tolbutamide, metyrapol, bupropion (all >98%) and the internal standard (IS) carbamazepine were purchased from Sigma-Aldrich Company (St. Louis, U.S.A.). HPLC grade acetonitrile and methanol were from Merck Company (Darmstadt, Germany). All other chemicals were of analytical grade. Ultra-pure water (resistance >18 mΩ) was prepared by a Millipore Milli-Q purification system (Bedford, U.S.A.).

Animals Male Sprague-Dawley rats (300±12g) were obtained from Shanghai SLAC Laboratory Animal Co., Ltd. The animal license number was SCXK (Shanghai) 2012–0005. All twenty rats were housed at Wenzhou Medical University Laboratory Animal Research Center. Animals were housed under controlled conditions (22°C) with a natural light–dark cycle. All experimental procedures were conducted according to the Institutional Animal Care guidelines and approved ethically by the Administration Committee of Experimental Animals, Laboratory Animal Center of Wenzhou Medical University.

Instrumentation and Conditions All analysis was performed with a 1200 Series liquid chromatograph (Agilent Technologies, Waldbronn, Germany) equipped with a quaternary pump, a degasser, an autosampler, a thermostatted column compartment, and a Bruker Esquire HCT mass spectrometer (Bruker Technologies, Bremen, Germany) equipped with an electrospray ion source and controlled by ChemStation software (Version B.01.03 [204], Agilent Technologies, Waldbronn, Germany).

Chromatographic separation was achieved on a 150 mm×2.1 mm, 5 μm particle, Agilent Zorbax SB-C18 column at 30°C. A gradient elution programme was conducted for chromatographic separation with mobile phase A (0.1% formic acid in water) and mobile phase B (acetonitrile) as follows: 0–4.0 min (10–80% B), 4.0–8.0 min (80–80% B), 8.0–9.0 min (80–10% B), 9.0–13.0 min (10–10% B). The flow rate was 0.4 mL/min.

The quantification was performed by the peak-area method. The determination of target ions were performed in selective ion monitoring mode (m/z 180 for phenacetin, m/z 271 for tolbutamide, m/z 268 for metyrapol, m/z 240 for bupropion and m/z 237 for IS, Fig. 1) and positive ion electrospray ionization interface. Drying gas flow was set to 7 L/min and temperature to 350°C. Nebuliser pressure and capillary voltage of the system were adjusted to 25 psi and 3500 V, respectively.

Preparation of Standard Solutions Stock solutions of 1.0 mg/mL each of phenacetin, tolbutamide, metyrapol, bupropion and IS were prepared in methanol. The working standard solutions of each analyte were prepared by serial dilution of the stock solution with methanol. All of the solutions were stored at 4°C and brought to room temperature before use.

The calibration standards were prepared by spiking blank rat plasma with appropriate amounts of phenacetin, tolbutamide, metyrapol, bupropion. Calibration plots of each probe drug were constructed in the range 10–2000 ng/mL for plasma (10, 25, 50, 100, 200, 500, 1000 and 2000 ng/mL). Quality control (QC) samples were prepared by the same way as the calibration standards, three different plasma concentrations (25, 400, and 1600 ng/mL). The analytical standards and QC samples were stored at −20°C.

Method Validation The selectivity of the method against endogenous interferences was verified by examination of the chromatograms obtained after the extraction of six different source blank rat plasma samples.

Standard curves, freshly prepared with each batch of QC and sample, were generated using a least-squares linear regression, with a 1/x-weighting factor for all the compounds. The lower limit of quantitation (LLOQ) was estimated in the process of calibration curve construction and defined as the lowest concentration for which precision was less than 20% and accuracy within 80–120%.

Intra-assay precision was evaluated by six replicates analysis of the three QC samples in one run. Inter-assay precision was evaluated by six replicates analysis of the QC samples on three consecutive days.

Recoveries at three QC levels were determined by comparing the peak areas of extracted plasma standards with the peak areas of post-extraction plasma blanks spiked with equivalent concentrations using six replicates.

The matrix effect was investigated at three QC levels using three replicates by comparing the peak areas of spike-after-extraction samples with neat standard solutions.

Pharmacokinetic Study Twenty male Sprague-Dawley rats (300±12g) were randomly divided to control group and chronic hydrogen sulfide poisoning group (n=6), the rats were placed in triad infected ark which was with the hydrogen sulfide gases to create a model of chronic hydrogen sulfide poisoning. The chronic hydrogen sulfide poisoning group rats were exposed to 20 ppm H₂S for 1 h twice per day for 40 d. Control animals were maintained under similar conditions, but without the H₂S exposure. Rats were allowed to eat and drink ad libitum except during the 1 h per day exposure.

After complete the modeling, the chronic hydrogen sulfide poisoning and control rats were injected the mixed 4 probe drugs with the 0.5 mL/kg dose through sublingual veins injection. The concentrations of phenacetin, tolbutamide, bupropion and metyrapol were 5 mg/mL, 1.25 mg/mL, 5 mg/mL and 1.2 mg/mL, respectively. The administration dose of the probe drugs phenacetin, tolbutamide, bupropion and metyrapol were 2.5 mg/kg, 0.75 mg/kg, 2.5 mg/kg and 0.6 mg/kg, respectively.

Blood samples (0.3 mL) were collected from the tail vein into heparinized 1.5 mL polythene tubes at 5, 15, 30 min and 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48 h after sublingual vein administration of probe drugs. The samples were immediately centrifuged at 13000 r/min for 5 min, and 100 μL plasma was obtained for each sample.

The plasma samples were extracted and measured by LC-MS. In a 1.5 mL centrifuge tube, an aliquot of 10 μL of the internal standard working solution (2.0 μg/mL) was added to 0.1 mL of collected plasma sample followed by the addition of 0.2 mL of acetonitrile. After the tube was vortex-mixed for 1.0 min, the sample was centrifuged at 15000 rpm for 10 min. The supernatant (5 μL) was injected into the LC-MS system for analysis.

Plasma probe drugs concentration versus time data for each rat was analyzed by DAS software (Version 3.0, Drug Clinical Research Center of Shanghai University of T.C.M. and Shanghai BioGuider Medicinal Technology Co., Ltd., China). The pharmacokinetic parameters of the test group and control
Fig. 1. Mass Spectra of Phenacetin (a), Tolbutamide (b), Metoprolol (c), Bupropion (d) and IS (e) in Selective Ion Monitoring Mode with ESI (+) Source
Fig. 2. LC-MS Chromatograms: (a) Blank Plasma; (b) Blank Plasma Spiked with Carbamazepine (IS); (c) Blank Plasma Spiked with Phenacetin; (d) Blank Plasma Spiked with Tolbutamide; (e) Blank Plasma Spiked with Bupropion; (f) Blank Plasma Spiked with Metoprolol

Table 1. Precision, Accuracy and Recovery for Probe Drugs in Rats Plasma (Mean±S.D., n=6)

<table>
<thead>
<tr>
<th>Probe drugs</th>
<th>Concentration (ng/mL)</th>
<th>Intra-day RSD (%)</th>
<th>Inter-day RSD (%)</th>
<th>Intra-day RE (%)</th>
<th>Inter-day RE (%)</th>
<th>Recovery (%)</th>
<th>Matrix effect (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenacetin</td>
<td>25</td>
<td>9.70</td>
<td>12.43</td>
<td>10.60</td>
<td>−11.60</td>
<td>92.56±6.32</td>
<td>93.41±7.33</td>
</tr>
<tr>
<td></td>
<td>250</td>
<td>8.67</td>
<td>6.39</td>
<td>−4.36</td>
<td>3.46</td>
<td>98.13±3.68</td>
<td>87.66±5.08</td>
</tr>
<tr>
<td></td>
<td>1600</td>
<td>4.19</td>
<td>6.52</td>
<td>5.04</td>
<td>2.78</td>
<td>100.63±6.79</td>
<td>93.45±1.06</td>
</tr>
<tr>
<td>Tolbutamide</td>
<td>25</td>
<td>6.30</td>
<td>6.26</td>
<td>8.67</td>
<td>9.21</td>
<td>91.46±7.23</td>
<td>87.94±6.84</td>
</tr>
<tr>
<td></td>
<td>250</td>
<td>4.23</td>
<td>6.94</td>
<td>−6.89</td>
<td>−7.44</td>
<td>100.24±8.44</td>
<td>89.25±7.56</td>
</tr>
<tr>
<td></td>
<td>1600</td>
<td>3.23</td>
<td>3.66</td>
<td>4.14</td>
<td>3.97</td>
<td>89.28±1.35</td>
<td>91.36±2.41</td>
</tr>
<tr>
<td>Bupropion</td>
<td>25</td>
<td>7.68</td>
<td>8.50</td>
<td>7.15</td>
<td>9.01</td>
<td>102.89±12.73</td>
<td>89.87±9.02</td>
</tr>
<tr>
<td></td>
<td>250</td>
<td>6.93</td>
<td>7.03</td>
<td>3.48</td>
<td>6.19</td>
<td>109.22±6.21</td>
<td>90.42±2.89</td>
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<tr>
<td></td>
<td>1600</td>
<td>4.75</td>
<td>3.07</td>
<td>−5.84</td>
<td>−3.34</td>
<td>99.81±2.48</td>
<td>99.34±3.03</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>25</td>
<td>12.76</td>
<td>10.35</td>
<td>9.07</td>
<td>9.32</td>
<td>90.31±8.83</td>
<td>95.63±6.47</td>
</tr>
<tr>
<td></td>
<td>250</td>
<td>9.68</td>
<td>6.60</td>
<td>2.72</td>
<td>−3.04</td>
<td>92.27±9.02</td>
<td>90.32±7.85</td>
</tr>
<tr>
<td></td>
<td>1600</td>
<td>5.81</td>
<td>3.46</td>
<td>−1.96</td>
<td>−2.14</td>
<td>91.22±5.37</td>
<td>93.15±3.21</td>
</tr>
</tbody>
</table>
group probe drugs with the t-test inspection were analyzed by SPSS 18.0 statistical software. A \( p < 0.05 \) was considered as statistically significant.

RESULTS

Method Validation

Figure 2 showed the typical chromatograms of a blank plasma sample, a blank plasma sample spiked with probe drugs and IS, and a plasma sample detected by LC-MS. No interfering endogenous substances were observed at the retention time of the analytes and IS. That demonstrates the chromatographic separation method have a good peak shape and resolution.

Calibration curves for four probe drugs were generated by linear regression of peak area ratios against concentrations, respectively. The calibration plot of the probe drugs in the range of 10–2000 ng/mL were, \( y = 0.0006x + 0.0202 \) (\( r = 0.9994 \)) for phenacetin, \( y = 0.0008x - 0.0037 \) (\( r = 0.9991 \)) for tolbutamide, \( y = 0.0017x + 0.0381 \) (\( r = 0.9982 \)) for bupropion, \( y = 0.0025x + 0.0616 \) (0.9985) for metoprolol. Each probe drug peak area ratio with concentration has a good linear relationship in the range of concentration. The LLOQ for each probe drug in plasma was 10 ng/mL.

Table 1 showed the results of intra-day precision, inter-day precision, accuracy and extraction recovery. The relative standard deviation (RSD%) of the four probe drugs in low, medium and high three concentrations were less than 15%. The intra-day relative error (RE%) ranged from –6.89 to 10.60%, the inter-day RE% ranged from –7.44 to 11.60%. The results demonstrate that the values were within the acceptable range and the method was accurate and precise. The extraction recoveries were ranged from 89.25 to 93.45%.

Table 1 showed the results of matrix effect, the percent nominal concentration were more than 85% or less than 115%. The results indicate that ion suppression or enhancement from the plasma matrix was negligible for this analytical method.

Pharmacokinetic Study

The main pharmacokinetic parameters after administration of phenacetin, tolbutamide, bu-
propion and metoprolol from non-compartment model analysis were summarized in Table 2. In the experiment for chronic hydrogen sulfide poisoning and control group, there was a statistically significant difference in the area under the curve from zero to infinity ($AUC_{0\rightarrow\infty}$), plasma clearance ($CL$) and maximum plasma concentration ($C_{max}$) for phenacetin ($p<0.01$) and bupropion ($p<0.05$), while there was no statistical difference for tolbutamide and metoprolol. As can be seen from Table 2, compared chronic hydrogen sulfide poisoning group with the control group, the pharmacokinetic parameters of phenacetin have changed, $t_{1/2}$ from the 0.959 h reduced to 0.610 h, but there was no statistical significance ($p>0.05$). $AUC_{0\rightarrow\infty}$ from the 1053.6 reduced to 667.6 ng/mL*h with significant difference ($p<0.01$); $CL$ from 2.292 increased to 3.832 L/h/kg, there was significant difference ($p<0.01$); $C_{max}$ varied from 1756.9 to 863.7 ng/mL, there was significant difference ($p<0.01$). Compared chronic hydrogen sulfide poisoning group with the control group, the pharmacokinetic parameters of tolbutamide have almost not changed, $t_{1/2}$ from the 14.574 h reduced to 12.708 h, and there was no statistical significance ($p>0.05$); $AUC_{0\rightarrow\infty}$ from the 1053.6 to 667.6 ng/mL*h with significant difference ($p<0.01$); $CL$ from 2.292 increased to 3.832 L/h/kg, there was significant difference ($p<0.01$); $C_{max}$ varied from 1756.9 to 863.7 ng/mL, and there was no statistical significance ($p>0.05$). Compared chronic hydrogen sulfide poisoning group with the control group, the pharmacokinetic parameters of metoprolol have almost not changed, $C_{max}$ varied from 73.8 to 64.1 ng/mL, and there was no statistical significance ($p>0.05$). Compared chronic hydrogen sulfide poisoning group with the control group, the pharmacokinetic parameters of bupropion have changed, $t_{1/2}$ from the 2.308 h reduced to 1.267 h, there was statistical significance ($p<0.01$); $AUC_{0\rightarrow\infty}$ from the 213.2 reduced to 136.9 ng/mL*h, with significant difference ($p<0.01$); $CL$ from 11.08 increased to 19.389 L/h/kg, there was statistical significance ($p<0.05$); $C_{max}$ varied from 159.0 to 96.2 ng/mL, there was statistical significance ($p<0.05$). The representative phenacetin, tolbutamide, bupropion and metoprolol concentration vs. time profiles of twelve rats were presented in Fig. 3. As could be seen from Fig. 3, the $AUC$ and $C_{max}$ of phenacetin and bupropion in chronic hydrogen sulfide poisoning group is lower than the control group, this result is consistent with the Table 2. The concentration–time curve diagram of tolbutamide and metoprolol in chronic hydrogen sulfide poisoning group almost coincided with control group.

**DISCUSSION**

**Chromatographic Conditions Development** Traditional methods often adopted high-performance liquid chromatography method for determination of probe drugs. However, simultaneous determination of a variety of drugs by HPLC method was not easy to obtain with high sensitivity. A sensitive, simple and specific LC-MS method could determine complex samples. Considering the chemical structure, physical and chemical properties of the four probe drugs used in this experiment, we choose acetonitrile with strong eluting ability as the organic phase. We used a gradient elution method for separation the probe drugs. We adjust the proportion of various solvents for the suitable retention time, and the final gradient elution programme was mobile phase A (0.1% formic acid) and mobile phase B (acetonitrile) as follows: 0–4 min (10–80% B), 4–8 min (80–80% B), 8–9 min (80–10% B).

Liquid–liquid extraction method was more common in the sample extraction, in preliminary experiments, we used ethyl acetate to extract the probe drugs, but the results were not satisfactory for low recovery. The organic solvent precipitation method was simple, convenient and fast. Organic solvent acetonitrile, ethanol and methanol were often used in organic solvent precipitation. In this study, acetonitrile was used to precipitate plasma samples for the better recovery than ethanol and methanol.

**Analysis of Experimental Results** Compared to the control group, chronic hydrogen sulfide poisoning group, the $AUC$ phenacetin go lower ($p<0.01$), $CL$ increases ($p<0.01$), $C_{max}$ becomes smaller ($p<0.01$), it indicate that chronic hydrogen sulfide poisoning will induce the activity of CYP1A2 enzyme. Compared to the control group, chronic hydrogen sulfide poisoning group, the pharmacokinetic parameters of tolbutamide have almost not changed, it indicate that the chronic hydrogen sulfide poisoning will not induce or inhibit the activity of CYP2C9 enzyme. The similar results was found in metopro-

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Table 2. Pharmacokinetic Parameters of Phenacetin, Tolbutamide, Metoprolol and Bupropion (Mean±S.D.), Control-Group n=6, Hydrogen Sulfide Poisoning-Group n=6

<table>
<thead>
<tr>
<th>Pharmacokinetic parameters</th>
<th>Control</th>
<th>H2S</th>
<th>Control</th>
<th>H2S</th>
<th>Control</th>
<th>H2S</th>
<th>Control</th>
<th>H2S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Half-life ($t_{1/2}$) (h)</td>
<td>0.959±0.630</td>
<td>0.610±0.165</td>
<td>1053.6±182.3</td>
<td>667.6±148.5**</td>
<td>1123.8±227.8</td>
<td>675.3±152.2**</td>
<td>0.800±0.251</td>
<td>0.785±0.169</td>
</tr>
<tr>
<td>$AUC_{0\rightarrow\infty}$ (ng/mL*h)</td>
<td>14.574±3.889</td>
<td>12.708±6.877</td>
<td>41008.0±7137.6</td>
<td>41518.9±4110.6</td>
<td>45633.7±9788.0</td>
<td>43901.3±3601.1</td>
<td>13.388±1.345</td>
<td>12.754±1.045</td>
</tr>
<tr>
<td>Average dwell time from zero to infinite ($MRT_{0\rightarrow\infty}$) (h)</td>
<td>0.830±0.190</td>
<td>3.832±0.700**</td>
<td>1.600±0.674</td>
<td>1.100±0.674</td>
<td>0.017±0.002</td>
<td>0.017±0.002</td>
<td>16.113±3.550</td>
<td>11.133±3.550</td>
</tr>
<tr>
<td>Apparent volume of distribution ($V$) (L/kg)</td>
<td>3.370±1.141</td>
<td>4.270±1.141</td>
<td>3.008±0.910</td>
<td>3.068±0.910</td>
<td>0.346±0.061</td>
<td>0.346±0.061</td>
<td>30.002±0.092</td>
<td>30.002±0.092</td>
</tr>
<tr>
<td>$C_{max}$ (ng/mL)</td>
<td>1756.9±272.5</td>
<td>863.7±251.1**</td>
<td>4069.2±771.5</td>
<td>3196.3±718.3</td>
<td>73.8±13.5</td>
<td>64.1±18.0</td>
<td>1053.6±182.3</td>
<td>667.6±148.5**</td>
</tr>
</tbody>
</table>

(Compared with the control group, *: $p<0.05$, **: $p<0.01$).

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Hydrogen Sulfide
lol, the pharmacokinetic parameters of metoprolol have almost not changed between control group and chronic hydrogen sulfide poisoning group, it show that the chronic hydrogen sulfide poisoning will not induce or inhibit the activity of CYP2D6 enzyme. Compared to the control group, the chronic hydrogen sulfide poisoning group, $t_{1/2}$ of bupropion reduced ($p<0.05$), $AUC_{0-t}$ reduced ($p<0.01$); $CL$ increased ($p<0.05$); $C_{max}$ becomes smaller ($p<0.05$), $MRT_{0-\infty}$ becomes smaller ($p<0.05$), it indicate that chronic hydrogen sulfide poisoning will induce the activity of CYP2B6 enzyme. The results demonstrated that chronic hydrogen sulfide poisoning could induce the activity of CYP1A2 and CYP2B6 of rats. The results may make sense for the clinical use of drugs for the people who work in pulp mill or pickled products manufacturing plant. The performance of liver may change who work in this environment for over a long period of time. Drugs that are metabolized through CYP1A2 and CYP2B6 enzyme given to the people after chronic hydrogen sulfide poisoning, it should need to pay close attention to changes in the plasma concentration to avoid drug interactions that may occur.

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