Effects of Medetomidine-Midazolam on Plasma Glucose and Insulin Concentrations in Laboratory Pigs

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(Received 9 August 1993/Accepted 6 January 1994)

ABSTRACT. Effects of medetomidine (40 μg/kg)-midazolam (0.2 mg/kg) on plasma glucose and insulin concentrations were evaluated in laboratory pigs. Intramuscular injection of medetomidine-midazolam induced a gradual hyperglycemic response associated with hypoinsulinemia which was much smaller than that by 80 μg/kg of medetomidine alone and was almost within a physiological fluctuation. These mild responses induced by medetomidine-midazolam were antagonized by use of an α₂-adrenoceptor antagonist atipamezole (160 μg/kg), therefore those changes were thought to be mainly attributed to the effect of medetomidine on α₂-adrenoceptors. A combination of medetomidine at a low dose and midazolam reduces undesirable effects, while providing more profound sedation than medetomidine alone in laboratory pigs.—KEY WORDS: glucose, medetomidine-midazolam, swine.


Medetomidine which is a newly developed α₂-adrenoceptor agonist provides the profound sedation in many species including pigs [4, 6, 11]. Medetomidine acts in a synergistic manner with midazolam in laboratory pigs and this combination induces more deep sedation than medetomidine alone, even if the dose of medetomidine is reduced to one half of its optimal dose, and even if the pigs are stimulated continuously during the induction phase [7]. Sedation induced by medetomidine-midazolam is deep enough to depress the aerosol reaction by most sensory stimuli [7]. In addition, this combination has minimal cardiopulmonary effects [9] and its effect is able to be quickly and smoothly antagonized by α₂-adrenoceptor antagonist atipamezole [8]. Therefore, this combination might be very valuable for chemical restraint in laboratory pigs.

However, α₂-adrenoceptors are widely distributed peripherally throughout the body in contrast to benzodiazepine receptors, not always having an inhibitory action and concurrent stimulation of these cause the undesirable effects [5]. One of the clinically apparent and easily assessable sign of peripheral or undesirable effects of α₂-agonists is hyperglycemia [3, 10] which is results from its action on the pancreas [2].

The purpose of this experiment was to evaluate the effects of medetomidine-midazolam on plasma glucose and insulin concentrations and to compare with that by an optimal dose of medetomidine alone. This study was also designed to evaluate an antagonistic effect of atipamezole on the changes induced by medetomidine-midazolam.

Twelve mixed breed pigs in good health were used in this study. Their mean age was 10.1 weeks (range 9 to 12 weeks) and mean body weight was 19.8 kg (range 18.5 to 22 kg). The pigs were fed a commercial ration (NS, Nisseiken Co., Ltd., Japan) once a day and given water ad libitum. After a week period of stabilization, the pigs were implanted 14G heparin-coated polyvinyl chloride catheters (Anthorn, Toray Medical Co., Japan) into the right lateral jugular vein under isoflurane anesthesia, and were assigned to two groups of six pigs each.

More than 7 days after implanting the catheter, the animals were fasted for 12 hr and placed in the sling. Six pigs were then administered saline solution (control) and other six pigs were administered medetomidine (Farmos Group Ltd., Finland) at a dose of 80 μg/kg of body weight (med80), 40 μg/kg of medetomidine and 0.2 mg/kg of midazolam (Dormicum, Yamanouchi Pharmaceutical Co., Japan) (med-mid) or med-mid and 160 μg/kg of atipamezole (Farmos Group Ltd., Finland) (med-mid-at) at a weekly interval. Atipamezole was injected 30 min after administration of med-mid. All the drugs and saline solution were injected into the cervical muscle.

Two ml of venous blood samples were then collected into glass tubes containing sodium fluoride through the implanted catheter 0 (base-line), 30, 60, 90, 120, 150, 180, 240 and 360 min after dosing for determination of plasma glucose concentrations. Another 2 ml of blood samples were collected 0 (base-line), 30, 60, 120 and 240 min after dosing into a glass tube containing EDTA-Na for determination of plasma insulin concentrations. After centrifugation, plasma was collected and frozen at −80°C until assayed.

Plasma glucose concentration was determined by glucose oxidase method (Glucose B-TEST, Wako, Wako Pure Chemical Industries, Ltd., Japan). Plasma insulin concentration was measured by a double-antibody enzyme-linked immunosorbent assay using a commercial kit (Glazyme Insulin-EIA TEST, Wako Pure Chemical Industries, Ltd., Japan). Since the commercial kit used in this study was developed to determine human insulin concentrations, some preliminary work was performed to determine the cross-reactivity of swine insulin. A solution of swine insulin (Sigma Chemical Company, U.S.A.) was prepared and standard dilutions (0, 5, 10, 125 and 250 μU of swine insulin/ml) were made with bovine serum albumin which was the matrix used in preparation of the assay kit standards to establish a standard curve. The standard curve generated by swine standards showed the comparable linearity with that by kit standards, although the reactivity was low in swine insulin. The lower limit in this assay system for swine insulin was 5 μU/ml. All samples were analyzed in duplicate.

The plasma glucose and insulin concentrations were statistically analyzed by two-way analysis of variance and
Fig. 1. Changes in plasma glucose concentration in pigs given saline solution (control; □), medetomidine-midazolam (med-mid; ○), medetomidine-midazolam-atipamezole (med-mid-atii; Δ), and 80 μg/kg of medetomidine alone (med 80; ●). Each symbol represents the mean (±SD) in each group (n=6). * = Significantly different from the base-line value, † = Significantly different from the values in all other groups, and □ = Significantly different from the values in a control and med-mid (p<0.05).

values after the drug administration were compared with base-line values using Scheffe’s multiple comparison procedure. Differences in the values among the groups tested at corresponding times were assessed by one-way analysis of variance and Scheffe’s multiple comparison procedure.

Figure 1 shows the change in plasma glucose concentrations in each group. Administration of med-mid induced a gradual increase in blood glucose, however its change was relatively small and no post-administration value was significantly different from the base-line value and from the values in control pigs. The change of plasma glucose concentration in pigs given atipamezole 30 min after the administration of med-mid was minimal, but there were no significant differences between the values in med-mid and those in med-mid-atii. On the other hand, the administration of medetomidine alone at the optimal dose (80 μg/kg) produced a significant change and induced moderate hyperglycemia, which reached a maximal level (more than 200 mg/dl) at 90 min after the injection.

Although the variations among the individuals were relatively large, plasma concentrations of insulin decreased significantly after the administration of med80 and the values at 30 and 60 min after the injection were below the lower limit in this assay system (Fig. 2). Plasma concentration of insulin in these pigs rapidly increased after that and recovered to or above the base-line level. Similar to the plasma glucose concentration, the change in plasma insulin concentration was relatively small in pigs given med-mid, and the values at 60 and 120 min after the drug administration were significantly higher than those in pigs given med80, although the value at 60 min after drug injection was significantly lower than that in control pigs. Administration of atipamezole significantly blocked the effect of med-mid 60 min after the drug administration (Fig. 2). It has been reported that α2-agonists induce hyperglycemia through the peripheral effect on α2-adrenoceptor in the pancreatic β-cells which are linked to the inhibition of insulin release in rats [A]. The data obtained in this study suggested that the changes in plasma glucose and insulin concentrations in pigs might be also induced through activation of α2-adrenoceptors by medetomidine.

In conclusion, the hyperglycemic effect induced by a combination of medetomidine at a low dose and midazolam was smaller than that by an optimal dose of medetomidine alone. This combination reduces the undesirable effects of medetomidine, while providing more profound sedation than medetomidine alone in laboratory pigs.

REFERENCES

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