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Midazolam and other benzodiazepines.

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Olkkola KT ; Ahonen J

Department of Anaesthesiology, Intensive Care, Emergency Care and Pain Medicine, Turku University Hospital, PO Box 52, kiinamylynkatu 4-8, FI-20521, Turku, Finland. klaus.olkkola@utu.fi

The actions of benzodiazepines are due to the potentiation of the neural inhibition that is mediated by gamma-aminobutyric acid (GABA). Practically all effects of the benzodiazepines result from their actions on the ionotropic GABA(A) receptors in the central nervous system. Benzodiazepines do not activate GABA(A) receptors directly but they require GABA. The main effects of benzodiazepines are sedation, hypnosis, decreased anxiety, anterograde amnesia, centrally mediated muscle relaxation and anti-convulsant activity. In addition to their action on the central nervous system, benzodiazepines have a dose-dependent ventilatory depressant effect and they also cause a modest reduction in arterial blood pressure and an increase in heart rate as a result of a decrease of systemic vascular resistance. The four benzodiazepines, widely used in clinical anaesthesia, are the agonists midazolam, diazepam and lorazepam and the antagonist flumazenil. Midazolam, diazepam and flumazenil are metabolized by cytochrome P450 (CYP) enzymes and by glucuronide conjugation whereas lorazepam directly undergoes glucuronide conjugation. CYP3A4 is important in the biotransformation of both midazolam and diazepam. CYP2C19 is important in the biotransformation of diazepam. Liver and renal dysfunction have only a minor effect on the pharmacokinetics of lorazepam but they slow down the elimination of the other benzodiazepines used in clinical anaesthesia. The duration of action of all benzodiazepines is strongly dependent on the duration of their administration. Based on clinical studies and computer simulations, midazolam has the shortest recovery profile followed by lorazepam and diazepam. Being metabolized by CYP enzymes, midazolam and diazepam have many clinically significant interactions with inhibitors and inducers of CYP3A4 and 2C19. In addition to pharmacokinetic interactions, benzodiazepines have synergistic interactions with other hypnotics and opioids. Midazolam, diazepam and lorazepam are widely used for sedation and to some extent also for induction and maintenance of anaesthesia. Flumazenil is very useful in reversing benzodiazepine-induced sedation as well as to diagnose or treat benzodiazepine overdose.

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