LETTER TO THE EDITOR

Should Midazolam Drug–Drug Interactions be of Concern to Palliative Care Physicians?

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I read the article *Drug Interactions in Dying Patients: A Retrospective Analysis of Hospice Inpatients in Germany*, written by Frechen et al. [1] with great interest. In the palliative care setting, drug–drug interactions (DDIs) must be of special concern, especially in end-of-life care when the patient's condition and organ functions deteriorate, the number of drugs taken often exceeds ten, and monitoring of the treatment becomes difficult. In the article, the authors reviewed the main drug combinations that may give rise to DDIs in patients undergoing palliative care. However, I would like to also draw special attention to the risk of DDIs with benzodiazepines, and particularly midazolam, which is classified by the Federal Union of German Associations of Pharmacists (ABDA) database as a substance with a low potential for DDIs.

It is well recognized that benzodiazepines carry a risk of serious pharmacodynamic interactions with many drugs that exert CNS depressant effects. Some of them are substrates of cytochrome P450 (CYP)3A and other CYP enzymes that raise additional risks of pharmacokinetic interactions through that system. These include diazepam, alprazolam, clonazepam, flunitrazepam, clorazepate and midazolam. The latter is a short-acting benzodiazepine and a CYP3A4 probe substrate. It is available for oral and parenteral administration mostly subcutaneously and intravenously and used more commonly in the palliative care setting in patients with difficulty swallowing and when death approaches, in the treatment of pain, dyspnea, anxiety, agitation and, more importantly, for brief and continuous palliative sedation in the management of refractory

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symptoms and intolerable suffering. The review of the literature shows that CYP3A inhibitors and inducers such as antifungal azoles (ketoconazole, itraconazole, fluconazole, voriconazole), erythromycin, ritonavir, rifampicin and carbamazepine, among others, significantly change the disposition of midazolam [2–8]. In one of the earlier studies of intravenous midazolam, the area under the plasma concentration-time curve (AUC) increased as much as fivefold after ketoconazole (strong CYP3A4 inhibitor) pretreatment, and intrinsic clearance decreased by 84 % [3]. Surely, the inhibition of midazolam metabolism was greater with oral administration (increase of total bioavailability from 25 to 80 % and 16-fold increase in AUC of midazolam) [3]. Such extensive alterations in midazolam pharmacokinetics should be expected to be of clinical relevance, which is supported by studies. The magnitude of the alterations in midazolam pharmacokinetics was well demonstrated in a study by Backman et al. [9], in which volunteers subsequently received itraconazole for 4 days and, after 2 weeks, rifampin (for a further 5 days). Midazolam was ingested before the first treatment, during and 4 days after itraconazole as well as 1 and 4 days after rifampin. During itraconazole treatment, the $AUC_{0-\infty}$ of midazolam increased eightfold, with prolongation of its elimination half-life from 2.7 to 7.6 h, while 1 day after rifampin treatment, the $AUC_{0-\infty}$ was greatly reduced to 2.3 % of the before-treatment value and 0.26 % of the value during CYP inhibitor treatment (an approximately 400-fold change in the AUC). The midazolam AUC was still considerably decreased when determined 4 days after rifampin cessation (13 % of the before-treatment value), which indicated that the risk of interactions outlasted the period of an inducer intake. In an interesting study, Hafner et al. investigated the pharmacokinetics of intravenous and oral midazolam after 14 days of co-administration of

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ritonavir (a potent CYP3A4 inhibitor) and St John's wort (a potent CYP3A4 inducer) [10]. The combined administration of the CYP3A4 inhibitor and inducer in that study resulted in a predominance of enzyme inhibition, with significant increases in the midazolam AUC to 180 and 412 % of the baseline value for intravenous and oral administration, respectively. When measured 2 days after withdrawal of the two CYP3A4 precipitants, the AUC of oral and intravenous midazolam decreased to 6 and 33 % of the level observed during combined administration, respectively, which reflects the prolonged effect of St John's wort on the metabolism of midazolam. This observation indicates even more complex outcomes of DDIs in clinical settings. The investigations clearly show a risk of considerable alterations in exposure to midazolam, also when used parenterally; it is important this be adequately recognized and dosages adjusted if required. In the clinical setting, other factors that might affect the pharmacokinetics and clinical effects of midazolam, including genetic polymorphism of CYP3A4/5 activity and deteriorating renal function in palliative care patients, among others, must be taken into account [11, 12].

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