Letter

Between benzodiazepine over-sedation and neurological damage

Jordan Kountchev, Romuald Bellmann and Michael Joannidis

Department of Internal Medicine, Division of General Internal Medicine, Medical Intensive Care Unit, Innsbruck, Austria

Corresponding author: Jordan Kountchev, jordan.kountchev@uibk.ac.at

Published online: 1 March 2005
This article is online at http://ccforum.com/content/9/3/303

Critical Care 2005, **9:**303 (DOI 10.1186/cc3493)

See related research by McKenzie *et al*., http://ccforum.com/content/9/1/R32

In the February issue of *Critical Care*, Dr McKenzie and colleagues [1] describe a new method to differentiate between midazolam over-sedation and neurological damage in the intensive care unit by measuring 1-hydroxymidazolam glucuronide (1-OHMG), an active metabolite of midazolam in serum.

1-OHMG is known to have sedative properties [2,3]. Although the method described (i.e. high-performance liquid chromatography coupled to mass spectrometric detection) might be highly specific and sensitive to detect and quantify the presence of the 1-OHMG, the presence of an active substance irrespective of its quantity can never be solely indicative of a given (patho-)physiological response. Development of drug tolerance is a basic principle in clinical pharmacology, the benzodiazepines being a paradigmatic example. Making dose–response relationship assessment *in vivo* is thus very problematic. It is dangerous to rely on parameters (1-OHMG), even if very carefully measured, without considering the physiological component/response, as potentially important decisions could result from a diagnosis such as neurological damage in the setting of critical illness. In this regard, flumazenil, a selective benzodiazepine receptor antagonist, will remain indispensable.

Authors' response

Catherine A McKenzie, William McKinnon, Declan P Naughton, David Treacher, Graham Davies, Gary J Phillips and Philip J Hilton

We thank Dr Kountchev and colleagues for their comments on our recent publication [1]. We do indeed recognise that drug tolerance is a well-known pharmacological property of benzodiazepines. This is borne out by the poor correlation between the plasma concentrations of midazolam or the metabolite 1-OHMG [4] and the degree of sedation. In the context of critical care when neurological outcome is uncertain, we remain convinced that it is highly desirable to establish whether the patient's neurological state can realistically be attributed to sedative drugs. Even more importantly, the likelihood of neurological damage is high when these are not detectable in the plasma – as we have shown in the paper.

We found the technique we describe clinically useful in the patients studied, which has informed our decision to seldom use midazolam in our intensive care unit due to the tendency for midazolam and its metabolites to accumulate. We did not dispute that flumazenil has a place in the assessment of potentially over-sedated patients but, as we pointed out, its abrupt action and lack of specificity has made it unpopular in our intensive care unit.

Competing interests

The author(s) declare that they have no competing interests.

References

1. McKenzie CA, McKinnon W, Naughton DP, Treacher D, Davies G, Phillips GJ, Hilton PJ: **Differentiating midazolam over-sedation from neurological damage in the intensive care unit.** *Crit Care* 2005, **9:**R32-R36.
2. Bauer TM, Ritz R, Haberthur C, Ha HR, Hunkeler W, Sleight AJ, Scollo-Lavizzari G, Haefeli WE: **Prolonged sedation due to accumulation of conjugated metabolites of midazolam.** *Lancet* 1995, **346:**145-147.
3. Hirata K, Matsumoto Y, Kurokawa A, Onda M, Shimizu M, Fukuoka M, Hirano M, Yamamoto Y: **Possible influence of midazolam sedation on the diagnosis of brain death: concentration of active metabolites after cessation of midazolam.** *Yakugaku Zasshi* 2003, **123:**811-815.
4. Oldenhof H, de Jong M, Steenhoek A, Janknegt R: **Clinical pharmacokinetics of midazolam in intensive care patients, a wide interpatient variability?** *Clin Pharmacol Ther* 1988; **43:**263-269.