

Title: AGE AND PLASMA PROTEINS INFLUENCE THE ACTION OF MIDAZOLAM

Authors: N. J. Halliday, F.F.A.R.C.S., J. W. Dundee, M.D., P. G. Loughran, F.F.A.R.C.S.
and K. W. Harper, F.F.A.R.C.S.

Affiliation: Department of Anaesthetics, The Queen's University of Belfast, Whitla Medical Building,
97 Lisburn Road, Belfast BT9 7BL, Northern Ireland.

Introduction. The injectable benzodiazepines, diazepam, flunitrazepam and midazolam, have an undesirable variability of action¹ when used as anaesthetic induction agents. When given alone there is a delay in onset of action compared with the rapidly acting thiopental and methohexital. In this study, for which local ethical committee approval was obtained, age and plasma protein concentration were examined as possible factors influencing the onset of action of a standard dose of midazolam. Some patients were also pretreated with either aspirin or probenecid, both of which may affect its plasma binding².

Methods. All patients were unpremedicated and otherwise healthy adults who had given informed verbal consent to participation. Initially 166 patients were studied, from whom 10 ml of blood was taken for plasma electrophoresis. Midazolam 0.3 mg/kg was injected into a large antecubital vein over 20 secs. The onset time was measured from the end of injection until the patient failed to respond to the verbal command 'Open your eyes'. If this did not occur by 3 min an induction time of 180 sec was recorded and anesthesia completed with a small dose of thiopental or inhalational agents.

In the second part, a further series of patients, aged under 50 years, were pretreated with 1 g i.v. aspirin given over 120 secs, with a further one min delay before the midazolam or with 1 g oral probenecid given one hour before the midazolam.

Results. A great variation in the onset of action of midazolam was noted. In the main group (mean age 45.5 yr \pm SEM 1.25) there was a significant negative correlation between patient age and onset time ($r = -0.49$; $P < 0.001$). Forty-three patients failed to lose consciousness by three mins and even excluding these there was still a clear negative correlation for age and onset time ($r = -0.46$; $P < 0.001$). The proportion of those over (94%) and under (60%) 50 years who were asleep by three mins differed markedly ($\chi^2 = 32.63$; $P < 0.001$). Furthermore, there was a significant difference between the mean onset time of those over (57.6 ± 1.34 (SEM)secs) and those under (113 ± 1.07 (SEM) secs) 50 years ($t = 3.24$; $P < 0.001$).

There was a strong positive correlation between the onset time and the plasma albumin concentration ($r = 0.5$; $P < 0.005$) and a less significant relationship to total plasma protein ($r = 0.35$; $P < 0.05$).

Pretreatment with either aspirin or probenecid produced a significant increase in the rapidity of induction of anesthesia (Table 1) and this is reflected by the higher incidence of patients losing consciousness within 3 mins. In a small number of patients we have demonstrated an increase in free midazolam following aspirin but this work is incomplete.

Discussion. This study shows that interpatient variability in response to midazolam is more marked in young patients. Forty per cent of those under 50 years were still awake 3 mins after injection of 0.3 mg/kg midazolam, compared with only 6 per cent in the older age group for whom it would seem to be a more acceptable induction agent.

Midazolam is 96-97% bound to plasma albumin. Small changes in binding may lead to relatively large alterations in the concentration of free, active drug and pharmacological activity. The relationship between albumin levels and induction time has previously been noted by Reves, Newfield and Smith³ but they did not standardise their dose of drug. Our results show that the onset of action of midazolam may vary because of different plasma protein binding from one individual to another or because of albumin bound drugs given beforehand.

Table 1. Mean (\pm SEM) onset time and mean log onset time in patients aged under 50 years who received aspirin 1 g, probenecid 1 g or no pretreatment.

Pretreatment (n)	Nil (97)	Aspirin (77)	Probenecid (44)
Mean time (secs)	113.7 \pm 1.07	85.4 \pm 7.17**	85.5 \pm 7.51*
Log time (secs)	2.0 \pm 0.03	1.9 \pm 0.03**	1.9 \pm 0.04*
% asleep by 3 mins	60	79	72

* $P < 0.01$; ** $P < 0.001$, compared with no treatment

References.

1. Dundee JW, Kawar P: Benzodiazepines in Anaesthesia, Pharmacology of Benzodiazepines. Edited by Usdin E, Skolnick P, Tallman JR Jr, Greenblatt DJ, Paul SM. London, Macmillan Press Limited, 1982, pp 313-328.
2. Moschitto LJ, Greenblatt DJ: Concentration-independent plasma protein binding of benzodiazepines J Pharm Pharmacol 35: 179, 1983.
3. Reves JG, Newfield P, Smith LR: Midazolam induction time: association with serum albumin. Anesthesiology 55: A259, 1981.