KINETICS OF HIGH-DOSE I.V. DIAZEPAM

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SUMMARY

The pharmacokinetics of high-dose i.v. diazepam were studied in two patients in an intensive care unit. The first patient received up to 240 mg of diazepam daily for 21 days while the second received 60 mg daily for 30 days. Plasma concentrations of diazepam and its major metabolite, desmethyldiazepam, were very large but, despite severe underlying disease and simultaneous administration of several other drugs, the half-lives of diazepam and desmethyldiazepam washout were consistent with those found in healthy persons. Washout half-lives in the first patient were, if anything, shorter than expected, possibly caused by simultaneous administration of phenobarbitone. Thus the kinetics of diazepam are apparently not altered by administration of large doses.

The kinetics of i.v. diazepam have been studied following single therapeutic doses in humans (Klotz et al., 1975; Mandelli, Tognoni, and Garattini, 1978; Greenblatt et al., 1980; Ochs et al., 1981a). However, very large doses of diazepam may be administered i.v. to patients for sedation in the intensive care unit (ICU). Little information is available on plasma diazepam concentrations or diazepam disposition in these circumstances. The report and study of diazepam kinetics and clinical effects during and after administration of very large doses i.v. to patients in an ICU.

CASE REPORTS

Patient 1

A 54-yr-old man was admitted to the intensive care unit with severe tetanus. Because of uncontrollable muscle spasticity and agitation pancuronium was given to allow tracheal intubation and assisted ventilation. During the first 21 days the patient received numerous drugs including fentanyl, biperiden (an anticholinergic agent), droperidol, promethazine, chlorpromazine, pethidine and a mixture of ergot alkaloids. The patient also received multiple i.v bolus doses of diazepam ranging from 60 to 240 mg per day (fig. 1). The doses were reduced and discontinued by day 21. In an attempt to enhance the elimination of diazepam and its metabolite by enzyme induction, phenobarbitone (up to 240 mg per day) was administered from day 14 to day 21.

Multiple venous blood samples were drawn from an indwelling central venous cannula during and after the period of diazepam administration.

Patient 2

A 43-yr-old man with chest trauma, and renal insufficiency which required haemodialysis, was admitted to the intensive care unit. To produce sedation for assisted ventilation, the patient received 60 mg daily of i.v. diazepam in multiple bolus doses for a period of 30 days. Additional drugs administered included dobutamine, cimetidine, gentamicin and opiate analgesics. Multiple venous blood samples were drawn from a central venous cannula over the 12 days after diazepam discontinuation.

Concentrations of diazepam and its major metabolite, desmethyldiazepam, were determined in all samples by electron-capture gas-liquid chromatography (Greenblatt, 1978; Greenblatt, Ochs and Lloyd, 1980). The apparent half-life for disappearance of diazepam and desmethyldiazepam after termination of dosage was determined by linear regression analysis.

RESULTS

Patient 1

Concentrations of diazepam and its major metabolite, desmethyldiazepam, were very large, consistent with the large daily doses (fig. 1). Steady-state plasma concentrations ranged from...
1000 to more than 5000 ng ml$^{-1}$, and increased approximately in proportion to the daily dose. After termination of diazepam therapy, the apparent half-life of diazepam "washout" was 17 h and that of desmethyldiazepam was 28 h.

Central nervous system (c.n.s.) depression persisted after diazepam therapy was stopped and spontaneous ventilation did not resume until 7 days after diazepam was discontinued. Similarly, the patient did not become fully oriented until 7–10 days after diazepam had been stopped. He was discharged from the hospital 20 days after discontinuation of diazepam (after 40 days of hospital treatment).

**Patient 2**

Large concentrations of diazepam (400–800 ng ml$^{-1}$) and of desmethyldiazepam (1000–5000 ng ml$^{-1}$) were achieved after administration of diazepam (fig. 2). After discontinuing diazepam treatment, the apparent half-life of diazepam was 43 h and that of desmethyldiazepam 78 h.

**DISCUSSION**

Large doses of i.v. diazepam were required to produce satisfactory sedation in these severely ill, agitated patients. Daily doses of up to 10 times the usual range for anxiolytic or muscle relaxant therapy were administered. Steady-state plasma concentrations were correspondingly large compared with those measured during prolonged therapy with usual doses (Greenblatt et al., 1981). However, large concentrations were necessary to produce adequate sedation in these severely agitated patients (Dasta et al., 1981). There was no evidence that these doses and plasma concentrations of diazepam and its major metabolite were associated with any untoward cardiovascular depression.

In the first patient, phenobarbitone was administered simultaneously in an attempt to enhance...
diazepam elimination and thereby reduce the likelihood of prolonged c.n.s. depression previously reported following long-term high-dose diazepam therapy of tetanus (Kendall and Clarke, 1972; Odu- sote, George and Femi-Pearse, 1976). Half-lives of diazepam and desmethyldiazepam washout after termination of administration were 17 and 28 h, respectively. The usual range of diazepam elimination half-life in otherwise healthy young males is 20–70 h, with a prolongation of half-life observed with increasing age (Klotz et al., 1975; Greenblatt et al., 1980; Ochs et al., 1981a). For desmethyl- diazepam, the usual range is 40–140 h, again with a prolongation observed in the elderly (Allen et al., 1980; Shader et al., 1981). Thus, washout of the two drugs in this patient was in fact more rapid than that generally observed in single-dose pharmacokinetic studies, suggesting that elimination was enhanced by the enzyme-inducing effects of phenobarbitone (Ohnhaus et al., 1979). Nonetheless, prolonged c.n.s. depression persisted for many days after discontinuation of diazepam. This could have been caused either by the underlying disease, or by persistence of diazepam and its metabolite after discontinuing administration. Since a precise relationship of plasma diazepam concentrations and clinical sedative effects has not been established, the cause of prolonged c.n.s. depression in this patient cannot be conclusively identified.

In the second patient, the washout half-lives of diazepam (43 h) and desmethyldiazepam (78 h) were within the range observed following single therapeutic doses in healthy individuals as described above. This was true despite the presence of advanced renal failure, which in previous studies has been shown not to impair the elimination of diazepam (Ochs et al., 1981b). Although simultaneous administration of cimetidine is known to impair diazepam clearance (Klotz and Riemann, 1980), it does not necessarily prolong diazepam half-life to a value exceeding the expected range.

The findings suggest that administration of high-dose i.v. diazepam leads to predictably large concentrations of diazepam and its major metabolite, desmethyldiazepam. There is no evidence of dose-dependent kinetics. However, the possibility of prolonged c.n.s. depression following termination of diazepam dosage should be considered.

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**REFERENCES**


### Cinétique du Diazépam Intraveineux A Fortes Doses

**RESUME**

La pharmacocinétique du diazépam i.v. à fortes doses a été étudiée chez deux patients de réanimation. Le premier patient a reçu des doses de diazépam atteignant 240 mg par jour pendant 21 jours et l'autre patient a reçu 60 mg/jour pendant 30 jours. Les concentrations plasmatiques de diazépam et de son principal métabolite, le déméthyldiazépam, étaient très élevées mais, malgré une pathologie associée très sévère et l'administration simultanée de plusieurs autres produits, les demi-vies d'élimination du diazépam et du déméthyldiazépam étaient du même ordre de grandeur que chez des individus bien portants. Chez le premier patient, les demi-vies d'élimination étaient même plus brèves que prévu, peut-être à cause d'une administration simultanée de phénobarbital. Ainsi la cinétique du diazépam n'est apparemment pas modifiée par l'administration de fortes doses.

### Cinetica del Diazepam en Altas Dosis i.v.

**SUMARIO**

Se estudió la farmacocinética del diazepam en altas dosis i.v. administrado a dos pacientes de la unidad de cuidados intensivos. El primer paciente recibió hasta 240 mg de diazepam cada día durante 21 días mientras que el segundo recibía 60 mg diariamente por 30 días. Las concentraciones de diazepam y de su principal metabolito, el desmetildiazepam, eran muy altas pero, a pesar de la severa enfermedad subyacente y de la administración simultánea de varias otras substancias, las vidas medias del escorrimento del diazepam y del desmetildiazepam fueron compatibles con las registradas en personas sanas. Las vidas medias del escorrimento en el primer paciente fueron, asco, más cortas de lo previsto, posiblemente a raíz de la administración simultánea de fenobarbitona. Entonces, la cinética del diazepam no se encontró alterada por la administración de altas dosis.