DELAYED RECOVERY FROM A SEDATIVE: CORRELATION OF THE PLASMA LEVELS OF DIAZEPAM WITH CLINICAL EFFECTS AFTER ORAL AND INTRAVENOUS ADMINISTRATION

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SUMMARY

Plasma levels of diazepam were obtained in student volunteers after both oral and intravenous administration. Correlation with clinical effects showed that after oral administration, the onset of drowsiness and relaxation after 10–15 minutes was associated with a rapid absorption of the drug. When diazepam was administered intravenously, a pronounced clinical effect was observed for one hour after injection. This was followed by recovery at 2 hours, but subsequently the subjects reported recurrence of clinical symptoms at about 6 hours. This reappearance of drug action was shown to coincide with the remobilisation of diazepam in the subject, supplemented by the slow build up of the metabolite Ro 5–2180 (desmethyldiazepam). It was not associated solely with the levels of Ro 5–2180. From these results it appears that patient recovery is not complete for several hours.

Diazepam administered either intravenously or orally is now an accepted drug in dentistry for allaying fear in apprehensive patients undergoing restorative or oral surgical procedures.

Plasma levels of diazepam in man following single doses have been studied by de Silva, Koechlin and Bader (1966) using a gas chromatographic procedure. The results were, however, sufficiently inconclusive to justify a further study. It was decided to repeat these experiments using a larger number of subjects and attempt to correlate the plasma levels with clinical effects.

The present study was conducted in two parts. In the first, plasma levels of diazepam were followed over a short time span (up to 2½ hours), following oral and intravenous administration. In the second part, the plasma levels were monitored over two days. Healthy male volunteers, aged 20–23, were used throughout.

PART ONE

Plasma levels following oral and intravenous administration, short time scale.

METHOD

Seven subjects were given diazepam 10 mg orally, and venous blood samples taken at intervals of 0.25, 0.50, 1.0, 1.5, 2.0 and 2.5 hours after drug administration. Twelve subjects received diazepam 10 mg intravenously, and ten subjects 20 mg by the same route, venous samples being taken at 3, 5, 10, 15, 30 and 60 min after administration. All blood samples were oxalated, centrifuged, and the plasma separated. The plasma samples were assayed for diazepam by a method based on that of de Silva and colleagues (1964). In this assay, the benzodiazepines, after extraction, are hydrolysed to the benzo-phenones, which are then analysed by electron capture gas chromatography.

RESULTS

Single oral doses of diazepam 10 mg produced peak levels of $0.3 \pm 0.08 \mu g/ml$ of the drug within 90 minutes (fig. 1). All subjects were relaxed and felt drowsy, with slurring of speech, 10–15 min after administration of the drug. Analysis of the plasma levels showed that very rapid absorption of the drug had occurred, approximately $0.15 \mu g/ml$ being present at 15 min. The drowsy and relaxed state persisted for 120 min, after which time all effects had disappeared. It is of interest that amnesia occurred during the period of activity of the drug. Without exception, the volunteers were unable to recall accurately the number of venous blood samples taken.

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Mean plasma level fall-off curves after administration of diazepam 10 mg and 20 mg by the intravenous route are shown in figure 2. After 3 min, a single 10 mg dose produced a plasma level of $0.8 \pm 0.21 \mu g/ml$, and a 20 mg dose a level of $1.1 \pm 0.18 \mu g/ml$. The subjects were relaxed, drowsy and unconcerned by the venous samples being taken, but all reacted to the sample taken at 60 min. Detailed questioning and a study of the reports written by the subjects 24 hours after the trial revealed that they were unable to recall any conversation or sample taken during the first 15–20 min.

The adverse effects occurring after 60 min, delaying the subject's discharge into the care of a responsible adult, and the unwanted effects occurring during the subsequent 24 hours are shown in table I. The subjects noticed a recurrence of the initial clinical symptoms at about 6 hours after injection, and began to feel tired at this time.

It is important to note that with the higher dose there was a considerable increase in the severity and duration of side effects. The number of subjects experiencing tiredness during the subsequent 24 hours:

![Fig. 1. Mean plasma level fall-off curve for 7 subjects following oral administration of 10 mg diazepam. The scatter shown refers to maximum and minimum plasma levels found in this group.](image1)

![Fig. 2. Mean plasma level fall-off curves for 1, 10 subjects following intravenous administration of 20 mg diazepam, and 2, 12 subjects following intravenous administration of 10 mg diazepam. Scatters shown refer to maximum and minimum plasma levels found in these groups.](image2)
DELAYED RECOVERY FROM A SEDATIVE

hours was increased from 3/12 to 7/10 after the higher dose. These results are similar to those obtained in a previous trial where diazepam was administered to apprehensive patients undergoing restorative dentistry (Baird and Flowerdew, 1970). As the metabolites of diazepam are pharmacologically active (Randall, Scheckel and Banziger, 1965), it was thought that the tiredness experienced by the subjects was due to a build up of these compounds over the 24 hours following administration. This seemed a reasonable assumption, as the plasma level of diazepam had fallen to a low level after 60 min (fig. 2). In order to confirm this, further studies were carried out, using an extended time scale.

PART TWO

Plasma levels following intravenous administration, long time scale.

METHOD

Five male subjects, two having participated in the first part of the trial, received a 20 mg intravenous

Fig. 3. Benzodiazepine fall off curves from subjects B — E following a 20 mg intravenous dose. — • — Diazepam, — △ — Ro 5-2180 (desmethyldiazepam), — ○ — Ro 5-5345 (hydroxydiazepam).
dose of diazepam, venous samples being taken before administration of the drug, and then over a period of 48 hours.

The analytical method used in the first part of this study provided a sensitive assay for diazepam, but suffered from a lack of specificity. The diazepam metabolites Ro 5-2180 (desmethyldiazepam) and oxazepam both hydrolyse to 2-amino-5-chloro-benzophenone (ACB). Similarly, diazepam and the hydroxylated metabolite Ro 5-5345 are both converted to 2-methylamino-5-chloro-benzophenone (MACB). In addition to this ambiguity, the method suffers from the disadvantage that there is a solvent impurity which elutes with a similar retention time to ACB, and a correction has therefore to be made to the ACB peak area. Furthermore, an entirely suitable internal standard was not available. Medazepam is suitable as an internal standard for gas chromatography, but cannot be used to check the extraction procedure, as, like diazepam, it is converted to MACB on hydrolysis.

In view of these shortcomings, assays in the second part of this study were carried out by gas chromatography of the intact benzodiazepines, as described by de Silva and Puglisi (1970). This assay makes use of medazepam as an internal standard. It is specific for diazepam and all its metabolites, and provides unambiguous data on the benzodiazepine plasma levels.

**RESULTS**

The levels of diazepam and its metabolites in four of the subjects are shown in figure 3. The curves obviously vary slightly from subject to subject, but show striking similarities. In all four the diazepam disappears rapidly from the circulating blood during the first two hours, and then reappears, rising to a peak at 6-8 hours after injection. The metabolite Ro 5-2180 (desmethyldiazepam) built up steadily over the 48 hour period, while Ro 5-5345 (hydroxydiazepam) was present only in small quantities at around 8 hours, or was not detected. The curve for diazepam obtained from the fifth subject (fig. 4) was somewhat different, in that the trough observed in the other cases was not present, but once again there were clearly two apparent half lives for diazepam. The reappearance of diazepam in the circula-
tion at about 6 hours is presumably responsible for the side effects reported by the subjects. These symptoms will obviously increase with a higher dosage of the drug.

DISCUSSION

These results suggest that after intravenous administration, a considerable proportion of diazepam is held at some storage site. It is probable that some storage occurs in adipose tissue, but release from a site of this type would be expected to result in a plasma level curve with a plateau, rather than a peak. The rapid initial fall off of the plasma diazepam, followed by the sharp rise to a peak at about 6 hours, indicates that the drug is somehow being removed from circulation, and then being rapidly reintroduced. One possibility is that diazepam participates in an enterohepatic cycle, being secreted in the bile duct, either as the free drug or as a labile metabolite. This would explain the observed time lag, release of diazepam presumably coinciding with release of bile from the gall bladder. Van der Kleijn and colleagues (1971) have drawn attention to the absorption of diazepam metabolites in the gastrointestinal tract following intravenous administration of diazepam in mice and dogs, and have suggested an enterohepatic process to account for the irregular fall off of diazepam and desmethyl-diazepam following continuous oral doses in man.

The appearance of a second, broader peak some 12 hours after intravenous administration implies that the cyclic process is repeated. This would be consistent with the considerable increase in the apparent half lives during the 6–48 hour period, compared with that observed during the period immediately following injection of the drug. After 8–10 hours clinical effects due to remobilised diazepam will be enhanced by the presence of significant quantities of Ro 5–2180.

It is clear from these results that full recovery from the effects of intravenous diazepam is not attained for many hours, and therefore suitable care and supervision of the patient are required after the initial apparent recovery.

It is intended to investigate further the process of diazepam storage, with a view to identifying storage sites and the mechanism of re-release of the drug.

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REFERENCES


RETABLISSEMENT RETARDE APRES UN SEDATIF: CORRELATION ENTRE LES TAUX PLASMATIQUES DE DIAZEPAM ET LES EFFETS CLINIQUES APRES ADMINISTRATION ORALE ET INTRAVEINEUSE

SOMMAIRE

On a déterminé chez des étudiants-volontaires le taux plasmatique de diazepam après administration orale et intraveineuse. La correlation avec les effets cliniques montra qu'après prise orale, le début de la somnolence et relaxation après quinze minutes s'associa avec une absorption rapide du médicament. Lorsque diazepam avait été administré par voie intraveineuse, on observa un effet clinique prononcé pendant une heure après l'injection. Le rétablissement suivait après 2 heures, mais les sujets rapportèrent ensuite une remanifestation des symptômes cliniques après environ 6 heures. Cette réapparition de l'effet médicamenteux coïncida avec la remobilisation de diazepam chez le patient, avec en supplément la lente formation du métabolite RO5-2180 (desmethyl Diazepam). Cela ne s'associa pas uniquement avec des taux de RO5-2180. Il ressort de ces résultats que le rétablissement du patient n'est pas complet avant plusieurs heures.

VERZÖGTERTE ERHOLUNG NACH EINEM SEDATIVUM: DIE PLASMASPIEGEL VON DIAZEPAM NACH ORALER UND INTRAVENÖSER VERABREICHUNG WERDEN IN BEZIEHUNG GESETZT ZU KLINISCHEN AUSWIRKUNGEN

ZUSAMMENFASSUNG


RESTABLECIMIENTO RETRASADO DESPUES DE UN SEDANTE: CORRELACION DE LOS NIVELES PLASMATICOS DEL DIACEPAM CON LOS EFECTOS CLINICOS DESPUES DE SU ADMINISTRACION ORAL E INTRAVENOSA

RESUMEN
Fueron obtenidos en voluntarios estudiantes los niveles de diacepam en el plasma después de su administración oral e intravenosa. La correlación con los efectos clínicos mostró que después de la administración oral el comienzo de la somnolencia y relajamiento después de 10-15 minutos estaba asociado con una absorción rápida del medicamento. Cuando se administra diazepam por vía intravenosa se observó un marcado efecto clínico durante una hora después de la inyección. Esto fue seguido por un restablecimiento a las 2 horas, pero después estos sujetos observaron una recurrencia de los síntomas clínicos después de aproximadamente 6 horas. Se mostró que esta reaparición de la acción del fármaco coincidía con una removilización del diafragma en el paciente, completada por la formación lenta del metabolito Ro 5-2180 (desmetildiacepam). No estaba asociada exclusivamente con los niveles de Ro 5-2180. Los resultados anteriores indican que el restablecimiento no es completo durante varias horas.

BOOK REVIEW


The growing number of small volumes on specialized subjects is to be commended in many respects. New material and detailed analysis can be conveyed faster and more cheaply than in a large general textbook. More than one publishing house now produces volumes on different topics at regular intervals. This book, in the International Anesthesiology Clinics series, is one of them. I have read it with both disappointment and concern, not because the subject is unimportant or because the book is totally bad (a chapter on atelectasis is first class), but because I believe there have been serious errors in briefing and editorial scrutiny. I shall give three different examples, but they are typical of many more.

The impression is immediate: figure I, covering half a page, is a drawing of an obstructed water pipe to illustrate airway narrowing. I do not think the condition has many features in common with an obstructed water pipe, but my complaint is that such a simple analogy could be adequately conveyed in a line of text. Chapter 3 begins: “It is tantamount to impossible to rhetorically separate the actual incidence of postoperative hypoxemia...”. I recognize immediately my own susceptibility to a literary lapse, but this should not have got through. The same contributor describes the Haldane apparatus as a device for measuring CO2 in blood samples. Dr Nunn is cited in this connection. The chapter on aspiration pneumonitis is so similar in many respects to a previous publication by Hamelberg and Bosomworth (1968) that it seems unnecessary to have reproduced the material.

Why have these faults arisen? Is it because the authors do not care, or the publishers are not jealous for their reputation? I cannot believe that either is true. Is it that, having set a deadline, there is unreasonable pressure on authors, editors and publisher to meet it? From my own limited experience of these exercises, I think this is more likely. Whatever the reason, those responsible should alter their ways. Otherwise, the standards of medical literature will decline.

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REFERENCE