DIAZEPAM: ROUTES OF ADMINISTRATION AND RATE OF ABSORPTION

A study of women with pre-eclampsia

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SUMMARY

Plasma diazepam concentrations were determined following oral, i.m. and i.v. administration to a group of pregnant women with pre-eclampsia and a group of normal pregnant women. Diazepam concentrations were greater following oral as compared with i.m. administration in the control group, who received a single 5-mg dose, and this confirms previous similar reports. In the patients with pre-eclampsia, who were pre-loaded with diazepam, the i.m. route provided much higher plasma diazepam concentrations than did the oral route. This was probably a result of reduced gastric motility and gastric secretion caused by diazepam which affected the absorption of subsequent diazepam administered orally, and it is unlikely that pre-eclampsia contributed to these differences. Mist. magnesium trisilicate seemed to improve the rate of absorption of diazepam from the intestine in five patients studied, although this effect is unlikely to have much clinical importance.

Diazepam is used extensively in current medical practice as an anxiolytic, anticonvulsant and sedative, and in obstetrics it is particularly useful for the sedation of patients with gestational hypertension, pre-eclampsia, and for the control of eclampsia (Lean, Ratnam and Sivasamboo, 1968; Leinzinger, 1971; Joyce and Kenyon, 1972; Ruoss, 1974). Recently there have been several conflicting reports concerning plasma diazepam concentrations following different routes of administration of a single dose for pre-medication. Baird and Hailey (1973) have found that i.m. injection produced a more rapid uptake and higher plasma diazepam concentrations compared with oral administration, and this would be expected with most preparations. However, Gamble, MacKay and Dundee (1973), Hillestad and colleagues (1974), Kanto (1974) and Gamble, Dundee and Assaf (1975) have reported the opposite finding, of higher plasma diazepam concentrations following oral administration of a single dose and these findings correlated with the clinical effects (Assaf, Dundee and Gamble, 1975).

Diazepam is insoluble in water but readily taken up by adipose tissue, and thus poor injection technique, particularly in the buttock where there may be a thick layer of adipose tissue overlying the gluteal muscles, may result in even slower uptake of the drug to the circulation (Gamble, Dundee and Assaf, 1975), in which about 95% is bound to albumin (Van der Kleijn et al., 1971).

There have been no reports of plasma diazepam concentrations in women with pre-eclampsia, in whom there is, characteristically, a reduced plasma albumin concentration, although Kanto, Erkkola and Sellman (1973) have shown that normal women in labour have plasma diazepam concentrations, following i.m. administration, similar to those of normal non-pregnant women. This paper reports the findings in a study of plasma diazepam concentrations in normal pregnant women and women with pre-eclampsia.

PATIENTS

Antenatal patients with mild or moderate pre-eclampsia who had been admitted to hospital for rest were studied. The criteria for inclusion were:

(1) A mean arterial pressure (Burton, 1965) (m.a.p.) greater than 105 mm Hg on at least two occasions after 20 weeks gestation.

\[
\text{m.a.p.} = \frac{\text{systolic} + (\text{diastolic} \times 2)}{3}
\]

(2) Proteinuria recorded on at least one occasion since admission to hospital (there was no quantitative assessment).

(3) Diazepam had been prescribed as part of the routine clinical management.

(4) No other disease.
(5) The patient had given her informed consent to
the study.

There were 13 patients in this group, of whom
three received diazepam by oral, i.m. and i.v. ad-
ministration on separate occasions, six by the oral
and i.m. routes only and four patients were studied
after administration by one route only, which gave
10 patients in both the oral and i.m. sub-groups and
five in the i.v. sub-group.

The control patients were pregnant women who
were either resting in hospital for reasons other than
hypertension, such as placenta praevia, or who had
been admitted for induction of labour. The criteria
for inclusion in this group were:
(1) A normal arterial pressure throughout the preg-
nancy (m.a.p. not more than 100 mm Hg) and no
overall increase of m.a.p. during the pregnancy in
excess of 15 mm Hg.
(2) No other disease.
(3) Informed consent.

There were 25 patients in this group: 10 received
diazepam orally, 10 by i.m. injection and five by i.v.
 injection, the numbers matching those in the subject
sub-groups.

The subjects and controls were not matched for
age or length of gestation.

None of the patients in the control group had taken
any diazepam or chemically-related preparations
before the study.

PROCEDURE
All patients received diazepam 5 mg either orally or
by i.m. or i.v. injection. This was arranged to coincide
with one of the times when the test patients were to
receive diazepam routinely; in the control patients
the diazepam was given instead of night sedation. In
addition five of the 10 control patients receiving oral
diazepam received 15 ml of mist. magnesium trisili-
cate B.P.C.; also, to assess any alteration in the rate
of absorption of diazepam and to exclude other
possible systemic effects on the plasma diazepam
concentrations, comparable numbers of patients in
the other sub-groups received 15 ml of mist. mag-
nesium trisilicate, though only two of the test
subjects receiving oral diazepam did so.

The i.m. injections were all given by the same
person (D. W. S.) into the upper outer quadrant of a
buttock through a 21-gauge × 3.8-cm needle inserted
up to the hub.

The i.v. injections were given into one of the large
veins in the antecubital fossa and subsequent blood
samples were withdrawn from the other arm.

Venous blood samples (5 ml) were taken at 0, 15, 30,
45, 60 and 90 min, anticoagulated and centrifuged
(5000 r.p.m. for 10 min) and the plasma was stored
at —17 °C within 2 h. Diazepam was estimated by
gas–liquid chromatography after benzene extraction
of heparinized plasma (Gamble et al., 1975). Albumin
was measured on EDTA plasma by a bromocresol
green binding in citrate buffer containing Brij 35.
The packed cell volume was measured on the EDTA
sample.

RESULTS
There were great individual variations in plasma
diazepam concentration within each group; this has
also been noted in other studies (Zingales, 1973;
Hillestad et al., 1974; Gamble, Dundee and Assaf,
1975).

All the test patients had been taking diazepam
before the study (5 mg twice or thrice daily for 1–25
days); therefore the initial blood samples all contained
significant quantities of diazepam. In order to
facilitate comparisons with the controls, the initial
pre-test concentration was subtracted from the
subsequent diazepam concentrations, so that the
increment of plasma diazepam was recorded.

The mean plasma diazepam concentrations for
each group were compared. The mean increments of

FIG. 1. Increments of plasma diazepam (ng/ml) above the
initial pre-test values: mean values for the test patients
following oral and i.m. administration, with significance
levels (n.s. = not significant).
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plasma diazepam following oral and i.m. administration to the test patients (fig. 1) revealed a much more rapid increase associated with i.m. injection and a higher mean concentration throughout the 90 min. The values were significantly different from those in the other groups at 15, 30 and 45 min. A similar comparison in the control patients (fig. 2) showed a more rapid increase and higher mean diazepam concentrations after oral administration.

Comparison of diazepam concentrations following i.m. administration in the two groups (fig. 3) shows similar curves with a steep rise initially. Following i.v. injection there were similar curves for the two groups, with a much steeper rise initially compared with the curves following i.m. injection.

Following oral administration, there were marked differences in diazepam concentration between the two groups (fig. 4), the increase of plasma diazepam being considerably greater in the controls. The differences were statistically significant at each point up to 90 min.
The control patients who had received mist. magnesium trisilicate B.P.C. with the oral diazepam appeared to absorb diazepam more rapidly and had higher mean plasma diazepam concentrations, although this part of the study involved only five patients and the differences were not statistically significant (fig. 5). Magnesium trisilicate did not affect the plasma diazepam concentrations of those patients who received i.m. or i.v. diazepam.

The packed cell volumes were measured using one sample from each patient at every study, but there was little variation and the wide range of diazepam concentrations was much greater than could be attributed to alterations of haemoconcentration between each study in any individual patient; thus the diazepam concentrations were not adjusted.

**DISCUSSION**

This study confirms the recent reports of higher plasma diazepam concentrations following oral compared with i.m. administration of a single dose. However, the findings are different in those patients with pre-eclampsia and who had been taking diazepam before the study, in whom diazepam appeared to be absorbed very slowly following oral administration and the increase in the drug concentration in the plasma was considerably less than that following the i.m. route.

The i.m. and i.v. routes of administration provided similar increases in plasma diazepam concentrations in both the test patients and the controls, and this fact would seem to justify the comparison of mean increases in diazepam concentration after oral administration in the two groups.

Pre-eclampsia is more likely to occur in women who are overweight, and fluid retention, with a further increase in weight, is a common feature of this condition. Therefore it was not surprising that the mean weight of the test patients was 9 kg more than that of the controls (table I) and their higher mean arterial pressure and lower plasma albumin concentration were to be expected. However, it is most unlikely that pre-eclampsia contributed to the differences in diazepam concentration found in this study, and the similarity of the results following i.m. administration would support this (fig. 3). All the test patients had been taking diazepam before the study and this seems to be the most significant factor responsible for the differences between the two groups of patients following oral administration.

Studies of the factors which influence the absorption of drugs have shown the importance of the rate of gastric emptying and intestinal motility (Nimmo et al., 1973; Finch, Kendall and Mitchard, 1974) and there have been several reports of reduced gastric secretion following the administration of some of the hypnotic, tricyclic and anxiolytic drugs, including diazepam (Birnbaum, Ben-Menachem and Schwartz, 1970; Birnbaum, Karmeli and Tefera, 1971; Birnbaum and Karmeli, 1974; Bennett et al., 1975; Lavoie et al., 1975). It is likely that these side-effects of diazepam were responsible for the delayed absorption following oral administration in the test patients.

There was no difference in the rate of absorption in the patients in this study who had been taking diazepam for less than 3 days, compared with longer periods of administration, but Birnbaum, Karmeli and Tefera (1971) found that a single i.m. dose of diazepam 10 mg was sufficient to depress gastric activity and secretion. Diazepam does not have any anticholinergic effect in vitro and it has to be assumed that it has some action on the autonomic control within the central nervous system. This effect of diazepam may be beneficial to patients who suffer from symptoms related to excessive production of gastric juices, but may also reduce the rate of absorption of other drugs taken concurrently.

Magnesium trisilicate may improve the rate of absorption of oral diazepam, although only five patients were studied. Even if this is confirmed by a larger study it is unlikely to be of much clinical importance.

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| Table I. Age (yr), weight (kg), mean arterial pressure (mm Hg), plasma albumin (g/litre) and gestation (weeks) at the time of study: mean values with SEM and significance levels (P) |
|-------------|-----------|-------------|--------------|-------------|
| Patients    | Age (yr)  | Weight (kg) | M.a.p.       | Albumin     | Gestation   |
| Test        | 30.2 ± 1.3| 79.0 ± 5.0  | 106 ± 1.7    | 37.3 ± 1.7  | 37.3 ± 0.8  |
| Control     | 25.5 ± 0.9| 69.9 ± 6.6  | 90 ± 1.4     | 39.0 ± 1.2  | 39.9 ± 0.2  |
| P           | < 0.005   | < 0.0025    | < 0.0005     | < 0.05      |
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REFERENCES

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DIAZEPAM: VOIES D'ADMINISTRATION ET TAUX D'ABSORPTION
Une étude portant sur des femmes affectées par une pré-éclampsie

RESUME
Les concentrations de diazépam dans le plasma ont été déterminées après l'administration orale, intramusculaire et intraveineuse de diazépam à un groupe de femmes enceintes atteintes de pré-éclampsie, ainsi qu'à un groupe de femmes enceintes normales. On a trouvé que les concentrations de diazépam étaient plus importantes après l'administration orale qu'après l'administration intramusculaire dans le groupe témoin, qui n'avait reçu qu'une seule dose de 5 mg, ce qui confirme les rapports similaires antérieurs. Dans le groupe de patientes atteintes de pré-éclampsie, qui avaient reçu une pré-dose de diazépam, l'administration intramusculaire a provoqué des concentrations de diazépam dans le plasma beaucoup plus fortes que celles produites par l'administration orale. Ceci est probablement dû à une motilité gastrique réduite et à une sécrétion gastrique provoquée par le diazépam, qui a affecté l'absorption des doses de diazépam subéquentes administrées oralement. Il est improbable que la pré-éclampsie ait contribué d'une manière quelconque à ces différences. Un brouillard de trisilicate de magnésium a paru améliorer le taux d'absorption du diazépam par l'intestin de cinq patientes, bien que cet effet puisse ne pas avoir d'importance clinique bien grande.

DIAZEPAM: VERABREICHUNGSWEGE UND ABSORPTIONSGESCHWINDIGKEIT
Studie von Frauen mit Prä-Eklampsie

ZUSAMMENFASSUNG
Bestimmt wurden die Plasma-Diazepamkonzentrationen nach oraler, intramuskulärer und intravenöser Verabreichung an eine Gruppe schwangerer Frauen mit Prä-Eklampsie und an eine Gruppe normal schwangerer

DIAZEPAM: VIAS DE ADMINISTRACION Y SU INDICE DE ABSORCION
Un estudio de gestantes con pre-eclampsia

Se determinaron las concentraciones plasmáticas de diazepam tras la administración oral, i.m. y e.v. a un grupo de gestantes con pre-eclampsia y un grupo de gestantes normales. Las concentraciones de diazepam fueron mayores tras la administración oral en comparación con la i.m. en el grupo testigo, que recibió una dosis única de 5 mg, y ello confirma anteriores informes similares. En las pacientes con pre-eclampsia, que fueron pre-dosificadas con diazepam, la vía i.m. proporcionó concentraciones plasmáticas de diazepam mucho más elevadas que con la vía oral. Ello fue probablemente resultado de una motilidad gástrica reducida y secreción gástrica causada por diazepam que afectó la absorción del diazepam subsiguiente administrado oralmente, y no es probable que la pre-eclampsia contribuyese a estas diferencias. Una mezcla de trisilicato magnésico pareció mejorar el índice de absorción de diazepam en el intestino en cinco pacientes estudiadas, aunque no es probable que este efecto encierre gran importancia clínica.