

These findings are important, since they are likely to indicate continuing cellular damage. It should be emphasized that any cause of major cellular necrosis might produce such effects and they should not be considered as specific indicators of rejection. They are of clinical significance, for they will produce a tendency to thrombosis, particularly at sites of vascular damage or of stasis in blood flow. Major vessels may be concerned, but thrombi were also found in the small vessels of the lung and gastrointestinal tract at necropsy in three patients. If hepatic vessels were obstructed the resultant ischaemia could contribute to further liver damage.

Both fibrinolysis and coagulation can be influenced by treatment with the appropriate inhibitors. Inhibitors of fibrinolysis may be dangerous when intravascular coagulation is in progress, but have been used in two patients. In Case 8 pre-existing hepatic damage had produced haematological changes very suggestive of intravascular coagulation. Major deficiencies could not be replaced by transfusion before operation and tranexamic acid was given empirically. The more logical choice of heparin was considered, but was rejected in view of the major vascular anastomoses to be made. Excision of the damaged liver removed the stimulus to coagulation, and this together with the therapy given prevented major bleeding. Gastrointestinal bleeding complicated the early course of case 11, and fibrinolysis was inhibited with aminocaproic acid. Bleeding stopped, but after a few days anaemia developed with all the characteristics of the microangiopathic haemolysis known to be sometimes associated with intravascular fibrin (Brain *et al.*, 1962; Baker *et al.*, 1968). It seems likely that the inhibition of fibrinolysis allowed the deposition of macroscopic fibrin. Three patients have been treated with heparin. This was given shortly before the death of the patient in Case 8, too late to affect the final outcome; to Case 11, when it appeared to decrease the severity of the microangiopathic haemolytic anaemia; and to Case 9 at the time of deep-vein thrombosis. It may be that continuous anticoagulants may improve the prognosis, but this has yet to be established.

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REFERENCES

- Alkjaersig, N., Fletcher, A. P., and Sherry, S. (1959). *Journal of Clinical Investigation*, **38**, 1086.
- Baker, L. R. I., Rubenberg, M. L., Dacie, J. V., and Brain, M. C. (1968). *British Journal of Haematology*, **14**, 617.
- Brain, M. C., Dacie, J. V., and Hourihane, D. O'B. (1962). *British Journal of Haematology*, **8**, 358.
- Calne, R. Y., *et al.* (1968). *British Medical Journal*, **4**, 541.
- Donaldson, G. W. K., Davies, S. H., Darg, A., and Richmond, J. (1969). *Journal of Clinical Pathology*, **22**, 199.
- Flanc, C., Kakkar, V. V., and Clarke, M. B. (1968). *British Journal of Surgery*, **55**, 742.
- Flute, P. T. (1964). *British Medical Bulletin*, **20**, 195.
- Hardisty, R. M., and Ingram, G. I. C. (1965). *Bleeding Disorders*, p. 255. Oxford, Blackwell Scientific.
- Ingram, G. I. C. (1961). *Journal of Clinical Pathology*, **14**, 356.
- Kakkar, V. V., Flanc, C., Howe, C. T., O'Shea, M., and Flute, P. T. (1969). *British Medical Journal*, **1**, 806.
- McFarlane, A. S., Todd, D., and Cromwell, S. (1964). *Clinical Science*, **26**, 415.
- McKay, D. G. (1968). *Proceedings of the Royal Society of Medicine*, **61**, 1129.
- Merskey, C., Kleiner, G. J., and Johnson, A. J. (1966). *Blood*, **28**, 1.
- Penick, G. D., Roberts, H. R., and Dejanov, I. I. (1965). *Federation Proceedings*, **24**, 835.
- Rodriguez-Erdmann, F. (1965). *New England Journal of Medicine*, **273**, 1370.
- Sharp, A. A., and Eggleton, M. J. (1963). *Journal of Clinical Pathology*, **16**, 551.
- Sherry, S. (1968). *Annual Reviews of Medicine*, **19**, 247.
- Starzl, T. E., *et al.* (1968). *Surgery*, **63**, 549.
- Von Kaulla, K. N., Kaye, H., Von Kaulla, E., Marchioro, T. L., and Starzl, T. E. (1966). *Archives of Surgery*, **92**, 71.
- Williams, R., *et al.* (1969). *British Medical Journal*, **3**,

Nitrazepam—a Safe Hypnotic

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Summary: In 27 patients nitrazepam (Mogadon) taken in acute overdosage produced no untoward effects except drowsiness, even when 80 tablets were consumed. A double-blind trial in patients in general medical wards established that nitrazepam was as effective as butobarbitone as a hypnotic. It is concluded that nitrazepam is a safe and effective hypnotic.

Introduction

The criteria for the acceptability of a hypnotic should be demanding. They obviously include a reasonable certainty that adequate sleep will be induced, but lack of confusion or hangover and absence of dependence, drug rashes, and other adverse effects are equally important. In addition the rapid rise in the incidence of self-poisoning with sedative drugs (Scottish Health Services Council, 1968) makes it highly desirable to have available an effective hypnotic which is safe in overdose. At first sight such an aim is a pharmacological paradox, as a drug which in therapeutic doses will effectively induce sleep is unlikely at the same time to be safe in overdose. This is certainly true of barbiturates (Setter *et al.*,

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1966), methaqualone (Matthew *et al.*, 1968), and glutethimide (Linton, 1966). Chloral hydrate is generally accepted as being less dangerous in overdosage, but is not well tolerated in therapeutic doses because of gastrointestinal side-effects (Laurence, 1966). This paper reports the effects of acute overdosage with nitrazepam (Mogadon) and assesses its efficacy as a hypnotic.

Acute Overdosage

During the past two years nitrazepam was involved in 47 instances of acute poisoning admitted to this unit. Only the 27 patients who ingested nitrazepam alone are considered here. In the 10 patients who had taken the greatest number of tablets the presence of nitrazepam or its metabolites in blood or urine was confirmed (Tompsett, 1968). The patients comprised three males and 24 females between the ages of 12 and 82 years. The number of tablets ingested and the level of consciousness of these patients on admission to hospital are shown in Table I. Twenty-five patients were fully conscious throughout; the duration of drowsiness in the remaining two was less than 12 hours.

TABLE I.—Level of Consciousness after Ingestion of Nitrazepam

No. of tablets ingested . . .	<10	10-	20-	30-	40-	50-	60-	70-	80-
No. of patients . . .	5	8	6	5	2	0	0	0	1

Two patients (one who took 10- tablets and one who took 80- tablets) were drowsy; the remainder were fully conscious.

There was no depression of respiration in any patient, even in one with severe chronic bronchitis. Comparison of the blood pressure on admission and after recovery suggested that a transient fall had occurred in four patients, but in no instance was active treatment required. One patient known to be in atrial fibrillation before taking 80 tablets of nitrazepam remained in that rhythm but showed no evidence of deterioration.

The failure of acute overdoses of nitrazepam, even up to 80 tablets, to induce other than light sleep cast doubt on the efficacy of this hypnotic in therapeutic doses. A clinical trial was therefore conducted comparing nitrazepam with both butobarbitone and a placebo.

Therapeutic Efficacy of Nitrazepam

Externally identical tablets of nitrazepam 5 mg., butobarbitone 100 mg., and placebo were prepared for a double-blind trial in a balanced design. As there are six possible orders in which the drugs could be prescribed, patients were allocated to one of these on entering the trial. Each patient was given each substance for a week in a dose of two tablets nightly. The trial continued until three patients in each order had completed it satisfactorily, thus providing full information on 18 patients.

Thirty-four patients who were willing to participate in the trial were selected from the general medical wards; each was thought likely to be in the ward for three weeks and to be sufficiently co-operative to supply the desired information. Eleven patients were discharged before completing the trial and five others were withdrawn (see below); their results have been discarded.

The median age of the 18 patients (12 men and 6 women) whose results were suitable for full analysis was 55 years (range 37 to 70 years). Twelve of these patients were recovering from acute myocardial infarction and three from cardiac failure; the remainder suffered from duodenal ulceration, duodenal carcinoma, and idiopathic epilepsy respectively.

Measurements

Duration of Sleep.—The night nurse in charge of the ward recorded each morning an assessment of the duration of each

patient's sleep during the previous night. She did so by marking appropriately a 12-cm. line which was labelled at 1-cm. intervals representing each hour. The nurse was unaware of the patients' scores on the quality of sleep.

Quality of Sleep.—Each patient recorded independently each morning an assessment of the quality of his sleep during the previous night by making a mark on a 100-mm. line. A mark at the extreme left (score=0) would indicate that no sleep had been obtained, and a mark at the extreme right (score=1) would denote "perfect" sleep. The patients' scores were measured (from the left) to the nearest millimetre and expressed on a scale from 0 to 1.

Results

Duration of Sleep (Nurses' Scores).—For many reasons 6% of the scores were missing. The distribution of those remaining was normal, and the mean nightly duration of sleep of the 18 patients on each drug is shown in Table II. Analysis of variance of the scores showed that the duration of sleep with nitrazepam or butobarbitone was significantly greater than on placebo. The small difference between nitrazepam and butobarbitone was not significant.

TABLE II.—Duration and Quality of Sleep after Nitrazepam (10 mg.), Butobarbitone (200 mg.), and Placebo

	Nitrazepam	Butobarbitone	Placebo	Significance of Difference
Mean nightly duration of sleep (hours) . . .	6.64	6.55	5.79	P=0.001
*Mean nightly quality score (range 0 to 1) . . .	0.809	0.805	0.619	P=0.001

* Calculated after arcsin transformation, but presented retransformed.

Quality of Sleep (Patients' Scores).—Six per cent. of these scores were also missing, and as the distribution of those obtained was markedly skew towards the "perfect" this was adjusted to normality by arcsin transformation before analysis (Snedecor and Cochran, 1967). The mean nightly score for the 18 patients on each drug is also shown in Table II. Analysis of variance of the scores showed that the quality of sleep was very significantly better when the patients were having nitrazepam or butobarbitone than when on placebo. Again there was no significant difference between nitrazepam and butobarbitone. The main effect of "weeks" in the analysis of variance was also significant ($F_{2,333}=10.3$; $P<0.001$). The mean score for each week, irrespective of the drug taken, showed significant improvement ($P=0.001$) as the patients progressed in the trial (week 1, 0.676; week 2, 0.758; week 3, 0.806).

Association Between Scores.—The product-moment correlation coefficient between the patients' and nurses' scores was +0.501 ($P=0.001$). Correlation coefficients were also calculated for each patient separately; 17 were positive, ranging up to +0.894; 12 of these were significant at least at the $P=0.05$ level of probability.

Dream Recall.—There was no noticeable difference in the number of patients with dream recall in the morning or in the vividness of dreams while having nitrazepam (compared with the week before or after nitrazepam).

Withdrawals from Trial.—Only one of the five patients withdrawn from the trial was removed because of possible toxic effects of the drug. This patient was a 67-year-old woman suffering from pyelonephritis. She developed daytime drowsiness and ataxia during the first week of the trial while on nitrazepam. Her blood urea was 68 mg./100 ml. Three patients requested withdrawal on account of poor sedation during the first week—one on each of the three preparations. One other patient also did so during the second week while on placebo, having slept well on nitrazepam during the first week.

Discussion

No adverse effects of nitrazepam on the haemopoietic system or renal and hepatic function has been noted (Jordan, 1965). Nor has this drug shown any incompatibility when used with other drugs in the treatment of epilepsy (Kryspin-Exner, 1966), thyrotoxicosis, cardiac failure, hypertension (Maibach, 1965), and diabetes mellitus (Wyss and Mäder, 1965). Dependence on, or addiction to, nitrazepam has not been observed (Franke, 1965; Bethune *et al.*, 1966), nor has there been any report of delirium or epileptic seizures on withdrawal of the drug such as may complicate the withdrawal of other hypnotics (Glatt, 1968).

Few reports of overdosage with nitrazepam have been recorded. Hirsch (1968) reported a 15-year-old girl who suffered from liver disease and ingested 26 tablets, Liske and Forster (1963) a 27-year-old woman who took between 24 and 30 tablets, Franke (1965) a man aged 40 who took 18 tablets, and Bethune *et al.* (1966) a boy aged 6 years who ingested 16 tablets and an obese woman who took 70 tablets. With one exception no effect of the overdose other than profound but rousable sleep was noted. The exception (the patient who took 70 tablets) did not even fall asleep. No depressant effect on the respiratory or the cardiovascular system was observed.

To these isolated instances we add the findings in 27 patients. Despite careful observation we could determine no significant effect of overdosage with nitrazepam other than minimal disturbance of consciousness, even in a patient who took 80 tablets. We have been unable to find an authenticated record of death due to poisoning by this hypnotic; the lethal dose for man remains unknown.

It is therefore evident that nitrazepam is a hypnotic which, tablet for tablet, is unsurpassed as yet in safety. This element of safety would, however, be valueless if it were not also shown that the drug had a hypnotic effect as adequate as barbiturate.

Many methods, including use of activity beds and continuous E.E.G. monitoring, are available for the assessment of hypnotic drugs. Nevertheless, as insomnia is a subjective state, a feeling beyond the observation of mere indicants, the paradigm should surely be the personal report of the patient. The language

offered to the patients in this trial for communication of their feelings is known to be reliable and valid (Aitken, 1969).

The clinical trial clearly showed that nitrazepam was superior to a placebo as a hypnotic drug, and that it was as effective as butobarbitone. There was consistency between the patients' reports on the quality of sleep and the nurses' assessments of the duration of sleep. The results are similar to those of another trial with a similar method of analysis comparing nitrazepam and sodium amylobarbitone in psychiatric patients (Davies and Levine, 1967).

We conclude that nitrazepam is an effective hypnotic which is safe in overdosage.

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REFERENCES

- Aitken, R. C. B. (1969). *Proceedings of the Royal Society of Medicine*. In press.
- Bethune, H. C., Burrell, R. H., Culpan, R. H., and Ogg, G. J. (1966). *New Zealand Medical Journal*, **65**, 613.
- Davies, C., and Levine, S. (1967). *British Journal of Psychiatry*, **113**, 1005.
- Franke, K. H. (1965). *Medizinische Welt*, **2**, 1658.
- Glatt, M. M. (1968). *British Medical Journal*, **3**, 376.
- Hirsch, W. (1968). *Therapie der Gegenwart*, **107**, 686.
- Jordan, B. (1965). *Médecine et Hygiène*, **23**, 249.
- Kryspin-Exner, K. (1966). *Wiener klinische Wochenschrift*, **78**, 121.
- Laurence, D. R. (1966). *Clinical Pharmacology*, 3rd ed., p. 164. London, Churchill.
- Linton, A. L. (1966). *Scottish Medical Journal*, **11**, 295.
- Liske, E., and Forster, F. M. (1963). *Journal of New Drugs*, **3**, 241.
- Maibach, E. (1965). *Therapeutische Umschau und medizinische Bibliographie*, **22**, 501.
- Matthew, H., Proudfoot, A. T., Brown, S. S., and Smith, A. C. A. (1968). *British Medical Journal*, **2**, 101.
- Scottish Health Services Council (1968). *Hospital Treatment of Acute Poisoning*. Edinburgh, H.M.S.O.
- Setter, J. G., Maher, J. E., and Schreiner, G. E. (1966). *Archives of Internal Medicine*, **117**, 224.
- Snedecor, G. W., and Cochran, W. G. (1967). *Statistical Methods*, 6th ed. Ames, Iowa State University Press.
- Tompsett, S. L. (1968). *Journal of Clinical Pathology*, **21**, 366.
- Wyss, S., and Mäder, A. (1965). *Schweizerische Medizinische Wochenschrift*, **95**, 338.

Growth Hormone Secretion in Growth-retarded Asthmatic Children

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Summary: The serum growth hormone response to Bovril was studied in 12 growth-retarded children with severe asthma, and was found to be normal. Eight children who were receiving corticosteroids had been small for their age before starting steroid treatment. It is concluded that there is no case for treating growth-retarded asthmatic children with growth hormone.

Introduction

Growth retardation which occurs in severely affected asthmatic children (Falliers *et al.*, 1963, and Norman, 1965) can be accentuated by the use of corticosteroid drugs (Kerrebijn and De Kroon, 1965). Now that a simple and reliable method of

evaluating growth hormone secretion is available in the Bovril test (Jackson *et al.*, 1968) we decided to study the human growth hormone (H.G.H.) responses of severely growth-retarded asthmatic children.

Materials and Methods

Twelve patients who were attending the asthma clinic at the Hospital for Sick Children, Great Ormond Street, London, and showed growth retardation were studied (see Table). At the time of H.G.H. assay the heights of eight patients were below the third percentile, those of three were on the third percentile, and that of one on the fifth percentile, while all showed retardation of skeletal maturation. Two of the 12 patients were girls and 10 were boys; their ages ranged from 7.3 to 16.5 years (mean 12.6 years). All of them were severely asthmatic, but 10 also had had or were suffering from eczema and six from hay-fever. Corticosteroids, in doses of prednisone ranging

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