Oral Pre-anaesthetic Medication with a New Benzodiazepine Hypnotic*

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SUMMARY

A new benzodiazepine derivative (Ro 5-4200) was used as a hypnotic in a pilot study on 30 patients the night before an operation. The dosage used was 2 mg (1 tablet). Results proved very encouraging, and it was then decided to conduct a controlled double-blind trial comparing Ro 5-4200, phenobarbital 100 mg and a placebo in 150 patients (50 patients each way). At a dosage of 2 mg Ro 5-4200 produced significantly better results than phenobarbital and the placebo as an oral, sleep-inducing premedication.

S. Afr. Med. J., **47**, 109 (1973).

The investigation of Ro 5-4200 (flunitrazepam) as a premedication before surgery was undertaken when, on completion of a pilot study, it was noted that Ro 5-4200 had interesting possibilities. The drug seemed to work fast and well. The patients slept soundly and there were minimal side-effects. No clinical evidence of interference with any of the anaesthetic agents used was noted.

According to the manufacturers (Roche Products), Ro 5-4200 is a benzodiazepine derivative, possessing marked sedative, muscle relaxant and spasmolytic properties in animal experiments. Tested extensively in animal experiments, it had negligible effects on blood pressure and very little effect on the ECG. The cardiac rate was slightly reduced. High doses diminish the vasoconstrictor effect of noradrenaline, histamine and acetylcholine in cats. No measurable effect on respiration could be demonstrated.

The drug was well tolerated, and in normal doses did not cause any changes in blood picture or blood chemistry in animals or man.

MATERIALS AND METHOD

The studies were done on patients seen in private anaesthetic practice.

Pilot Study

The drug was given to 30 patients at random the night before surgery, and the sister on night duty was asked to complete a form for each patient and note the following details: (*i*) time elapsed until onset of sleep; (*ii*) duration of sleep; (*iii*) depth of sleep; and (*iv*) state at awakening.

The sister in charge was asked to assess the effectiveness of the tablet. The patient was also asked the next morning to assess the value of the tablet, and thirdly, the investigator judged the results obtained by questioning the patient and studying the information noted on the questionnaires by the night sister.

The results obtained showed that Ro 5-4200 had a very good hypnotic effect and it was then decided to conduct a double-blind investigation (Tables I and II).

TABLE I. TRIAL POPULATION AND DISTRIBUTION

	Ro 5-4200 pilot study	Double-blind study		
		Ro 5-4200	Phenobarbital	Placebo
Age (average)	**39,7 years (16 - 61 range)**	**44 years (22 - 78 range)**	**34 years (17 - 63 range)**	**38 years (19 - 70 range)**
Male	3	18	9	9
Female	27	32	41	41
Type of operation:				
Vaginal hysterectomy	6	4	6	7
Abdominal hysterectomy	5	13	4	6
Other abdominal operations	5	14	17	11
Other minor operations	14	19	23	26

*Date received: 26 July 1972.

TABLE II. RESPONSE TO THERAPY

		Double-blind study		
	Ro 5-4200 pilot study	Ro 5-4200 (50 patients)	Phenobarbital (50 patients)	Placebo (50 patients)
Onset of sleep				
— 20 minutes	15 (50%)	25 (50%)	12	7
— 45 minutes	11 (36,6%)	21 (42%)	16	13
> 45 minutes	4 (13,3%)	4 (8%)	22	30
Duration of sleep				
> 6 hours	25 (83,3%)	41 (82%)	23	20
4 - 6 hours	4 (13,3%)	5 (10%)	11	6
< 4 hours	1 (3,3%)	4 (8%)	16	21
Depth of sleep				
Did not wake up	21 (70%)	26 (52%)	14	6
Woke up once	6 (20%)	11 (22%)	15	10
Woke up several times	3 (10%)	13 (26%)	21	29
State at awakening				
Fresh	13 (43,3%)	30 (60%)	24	20
Tired	5 (16,6%)	10 (20%)	12	15
Drowsy	12 (40%)	10 (20%)	14	7
Investigator's rating				
Excellent	Not done	17 (34%)	5	2
Very good	Not done	14 (28%)	11	3
Good	Not done	12 (24%)	7	8
Moderate	Not done	3 (6%)	12	6
Poor	Not done	4 (8%)	15	31

Double-Blind Investigation

Sealed and invidually numbered packets containing either Ro 5-4200 tablets (50 packets), or 100 mg phenobarbital tablets (50 packets), or placebo tablets (50 packets), were issued on randomized basis to 150 patients the night before surgery, noting the number of the tablet against the name of the patient and the questionnaire. The contents of the packet were unknown to the patient, sister or investigator. The latter was in possession of a sealed code in case it was necessary to ascertain the identity of any tablet at any time.

The sister was instructed to give the patient 1 Mandrax tablet 2 hours after having received the trial tablet, if the patient was still unable to sleep, and note this on the case-history form. As in the pilot study, the night sister was asked to fill in the case-history form for each patient. The mental state of each patient was also clinically assessed by the investigator, e.g. nervousness, tenseness, agitation, etc., and also whether the patient was normally in the habit of taking sleeping tablets, other drugs, alcohol, etc. The trial population of each therapy group was comparable in every clinical parameter used for this assessment.

The morning before surgery the patient was questioned briefly as to the effect of the tablet and the response rated, in correlation with the completed details, as excellent, very good, good, moderate or poor.

RESULTS

An analysis of the results clearly shows the excellent response obtained with Ro 5-4200 in both the pilot study and double-blind study, with 50% of patients asleep in less than 20 minutes, and well over 80% in less than 45 minutes. Over 80% of patients slept for more than 6 hours. In the double-blind study 60% of patients receiving Ro 5-4200 felt fresh on awakening, and 86% of the patients slept very well (excellent, very good or good) compared with a 46% response on phenobarbital, and a 26% response on the placebo (Table II).

DISCUSSION

The results obtained from this investigation clearly indicate that Ro 5-4200 has very definite therapeutic value as a sleep-inducing agent. Results also clearly demonstrated that patients on a placebo (42%) and phenobarbital (32%) slept poorly. Patients entering a hospital for surgery definitely require a hypnotic the night before surgery.[1,2] One must recognize that the majority of these patients are only temporary insomniacs, who, under normal circumstances, sleep without the help of hypnotics, but who, under abnormal conditions such as being in hospital, require therapeutic support (transient insomnia).

No serious side-effects were noted in any of the groups, and Ro 5-4200 had no apparent effect on the anaesthetic *per se*. About 20% of the patients on Ro 5-4200 were drowsy on awakening, but no classical hangovers were noted.

Lastly, it will be noted that the trial population consisted mostly of female patients. This can be explained by the fact that patients receiving the tablets were mostly on gynaecological operating lists.

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REFERENCES

1. Jolly, C. (1965): Lancet, **1**, 42.
2. Murray, W. J., Bechtoldt, A. A. and Berman, L. (1968): J. Amer. Med. Assoc., **203**, 327.