Sleep and Hypnotics: Further Experiments

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Summary: Two experiments compatible with that used to investigate the effect of clinical doses (200 mg.) of amylobarbitone were set up to investigate the effects of clinical doses of chloral hydrate (800 mg.), dichloral phenazone (1,300 mg.), and Mandrax (methaqualone 250 mg. and diphenhydramine 25 mg.) over a period of one to two weeks.

Four healthy male subjects were used in each experiment and received placebo or drug throughout a period of six to eight weeks when control records, drug records, and drug withdrawal records were obtained.

Chloral hydrate was found to depress rapid eye movement (R.E.M.) sleep appreciably though less consistently than amylobarbitone. No withdrawal R.E.M. sleep rebound was found.

Neither dichloralphenazone nor Mandrax was found consistently to depress R.E.M. sleep, though occasional nights when R.E.M. sleep was low occurred more often with Mandrax.

In the light of other experiments it is postulated that there exists a “threshold” in the dose of a hypnotic, and that when this is exceeded the drug will produce R.E.M. reduction. Thus it may be possible to prescribe a drug which is clinically useful while avoiding withdrawal effects.

Introduction

The great expansion during the past 15 years of information on the measurement of sleep has prompted further research into the effects of hypnotic drugs (Oswald and Priest, 1965; Evans et al., 1968; Kales et al., 1968, 1969).

Sleep is composed of two regularly alternating physiological states: (1) orthodox sleep, characterized by regularity of physiological indices and relative absence of mental activity, and (2) paradoxical or rapid eye movement (R.E.M.) sleep, in which there is great irregularity of many physiological measures and in which the bulk of dreaming occurs (Dement and Kleitman, 1957; Jouvet, 1967). Orthodox sleep is further divided into four stages, and during much of adult life R.E.M. sleep is usually found to occupy about 24% of total sleep.

Sodium amylobarbitone has been the drug most used to examine the effects of a barbiturate on sleep (Oswald and Priest, 1965; Evans et al., 1968). In clinical doses it produced an immediate alternation in the relationship of orthodox sleep to R.E.M. sleep. Orthodox sleep was enhanced and there was considerable depression of R.E.M. sleep. During continued administration the amount of R.E.M. sleep approximated towards baseline values—a “tolerance” phenomenon. Stopping the drug produced a fluctuant excess of R.E.M. sleep which subsided over several weeks—a “rebound” phenomenon—and in the larger dose experiments this R.E.M. sleep excess was associated with nightmares (Oswald and Priest, 1965). This persistent state may explain the difficulties experienced in withdrawing the drug in some patients.

Though many patients may continue with the drug for long periods without attendant difficulties (Johnson and Clift, 1968), it would seem desirable that hypnotics should be free from withdrawal effects if this is possible.

The effects of various non-barbiturate hypnotics on sleep have been studied, but results are conflicting. Oswald and Priest (1965) found that 15 mg. of nitrazepam did not differ from amylobarbitone in its effects on R.E.M. sleep, though Tissot (1965) reported that nitrazepam enhanced R.E.M. sleep. Kales et al. (1968) showed that glutethimide 500 mg. and methyprylon 300 mg, also depressed R.E.M. sleep, and their withdrawal was accompanied by a R.E.M. sleep rebound. Kales et al. (1969) reported that while 300 mg. of methaqualone depressed R.E.M. sleep 150 mg. of the drug had no appreciable effects. Davison (1969) stated that Mandrax, a combination drug containing methaqualone 250 mg. and diphenhydramine 25 mg., also had no significant effect on R.E.M. sleep. Kales et al. (1969) reported that chloral hydrate in doses of 500 mg. and 1 g. did not appreciably affect R.E.M. sleep. Lehmann and Ban (1968) found that chloral hydrate (650 mg.) disturbed R.E.M. sleep insignificantly in comparison with quinalbarbitone (secobarbital) (100 mg.) or nitrazepam (10 mg.).

These observations raise some questions in relation to a current theory of drug withdrawal delirium (Gross et al., 1966; Greenberg and Pearlman, 1967). Drugs which on withdrawal can give rise to delirium—that is, alcohol, barbiturates and other hypnotics, meprobamate—have all been shown to produce R.E.M. depression and to be associated with an R.E.M. rebound in withdrawal (Gresham et al., 1963; Evans and Lewis, 1968; Oswald et al., 1969). It is an old observation (de Clérambault, 1910) that when chloral hydrate was withdrawn from addicts delirium resulted. This strongly suggests that chloral hydrate disturbs R.E.M. sleep.

In view of these conflicts two separate experiments were arranged to examine the effects of clinical doses of chloral hydrate, dichloralphenazone, and Mandrax (methaqualone 250 mg. and diphenhydramine 25 mg.).

Method

The experimental design follows closely that used to examine the effects of sodium amylobarbitone in clinical doses (Evans et al., 1968).

Four healthy men aged 21 to 26 were used in each experiment. Throughout the experimental period, six to eight weeks, they were instructed to refrain from alcohol and any medication and to keep regular hours when not recorded. The first recorded night in the laboratory was regarded as a “habituation” night (Mendels and Hawkins, 1967) and discarded. A series of six nights taken at intervals over a fortnight were used as baseline data. Five to eight intermittent night recordings were taken when the subjects were on hypnotics, and a similar number of recordings were obtained in the withdrawal period (for details see Table I and II).

On a recording night subjects reported to the laboratory at 22.30 hours. Silver disc electrodes were attached round the
eyes, to the scalp in the midline, and under the chin as described elsewhere (Evans et al., 1968). Bipolar montages were set up to record eye movements, encephalogram, and muscle tone on an encephalograph which ran continuously throughout the night. The record was analysed according to internationally agreed criteria (Rechtschaffen and Kales, 1968).

**Experiment 1.**—The subjects received cachers of either placebo or active drug every night throughout the experiment, whether they were recorded or not. Sodium lactose was used as a placebo, and 0.8 g. of chlorohydrate was chosen as a convenient dose of drug. Unfortunately Subject C developed a peridural abscess during the late control period, and he and Subject D were therefore left on placebo for a further week as Subject C required other medication. Subjects A and B received the drug for 13 consecutive nights while Subjects C and D took the drug for six nights. The withdrawal period on placebo was monitored for 13 nights. Cachers were taken at 23.00 hours.

**Experiment 2.**—After a series of habitation and baseline nights on placebo, four different subjects received either dichloralphenazone (1-3 g) or Mandrax by double-blind design. The drug was continued for 14 nights and a further series of records were obtained during withdrawal while the subjects were again on placebo. All cachers were taken at 23.00 hours.

**Results**

**Experiment 1.**—The data are presented in Table I. Chloral hydrate was found to disturb the balance of orthodox to R.E.M. sleep. R.E.M. sleep was depressed in all four subjects during the first two or three nights on the drug, and this depression was found to be significant at the 0.05 level (t = 13.6222) with the statistical procedure outlined previously (Lewis and Evans, 1969). This R.E.M. depressing effect was found usually in the first two to three hours of sleep, leading to an increased delay to the first R.E.M. period and absence of R.E.M. activity in the first two hours of sleep. Occasional later nights show R.E.M. depression but there is overall a return to baseline values. This drop in R.E.M. sleep is accompanied by an increase in stages I and II of orthodox sleep and there is an increase of changes on stages III and IV of orthodox sleep. Taking all four subjects together there is a tendency for the number of arousals and time awake to decrease on the drug, but there was no discernible alteration in the delay to sleep (d).

**Experiment 2.**—The data are outlined in Table II. Neither drug in clinical dose had pronounced or consistent effects on R.E.M. sleep. Subjects A and B had isolated nights when R.E.M. sleep was reduced, but there were no overall significant changes in the dimensions. Because of an increase in fast activity in the electroencephalograms of Subjects A and B in association with these low R.E.M. sleep nights, it was obvious that the drug received by Subjects A and B was different from that received by Subjects C and D. Correspondingly Subject B had a significantly raised R.E.M. sleep percentage on the first withdrawal night and Subject C had a raised R.E.M. sleep time on the second withdrawal night, though no consistent withdrawal state was found.

**Discussion**

In clinical doses these hypnotics disturb the balance of orthodox and R.E.M. sleep less than a clinical dose of

![Table I](image-url)
amobarbital and amytal (Evans et al., 1968). Though 0.8 g of chloral hydrate did significantly depress R.E.M. sleep in four subjects over the first two to three days, no definite rebound of R.E.M. sleep was observed when the drug was stopped.

Mandrax (Subjects A and B) did produce occasional nights of low R.E.M. sleep time, but the effect was erratic. On only one night for Subjects C and D was R.E.M. time reduced, and the effect of dichloralphenazone was to make the fluctuations in R.E.M. sleep time more apparent. No rebound of R.E.M. sleep was seen when either of these drugs was withdrawn. This result differs from that of Kales et al. (1969), who found that 1 g of chloral hydrate failed to have any significant effects on R.E.M. sleep, but partly confirms his finding that 150 mg of methaqualone had no significant effects on R.E.M. sleep. Nevertheless, he found that 300 mg of methaqualone did depress R.E.M. sleep significantly. These observations suggest that in order to depress R.E.M. sleep a given drug may need to exceed a "threshold" which may vary in species, individuals, and over a period of time. The threshold for methaqualone may be between 250 and 300 mg. In our subjects 0.8 g of chloral hydrate must be sufficient to exceed this threshold, though Kales et al. found that 1 g was insufficient.

Further statistical analysis shows evidence of individual differences within the group on the chloral. R.E.M. sleep depression in Subjects A and B is significant at a level of P < 0.01 (t = 59–56). In the case of Subjects C and D the depression is less significant (P > 0.05, t = 13–622). There is no evidence that this is a dose-weight effect.

Thresholds—that is, dose response effects—have been found in administration of other drugs not primarily hypnotics; mono-amine oxidase inhibitors (Akindele et al., 1970), chlorpromazine (Lewis and Evans, 1969), and chlorpromazine (Evans and Lewis, 1968). The existence of such a threshold varying in individuals may explain the conflicting results obtained from various studies of non-barbiturate hypnotics.
Osteotomy of the Lesser Trochanter for Rheumatoid Arthritis of the Hip

J. A. FIXSEN, M. CHR., F. R. C. S.; M. F. SULLIVAN, F. R. C. S.

References


Summary: Forty-eight operations of osteotomy of the lesser trochanter in 45 patients were reviewed after an average of three and a half years. The results have been obtained by proved rheumatoid arthritis eight obtained complete relief of pain and two partial relief. Of 38 hips affected by osteoarthritis 16 had complete relief and 17 partial relief.
The results suggest that osteotomy of the lesser trochanter deserves a more extended trial in cases of proved rheumatoid arthritis of the hip joint.

Introduction

Release of the pelvifemoral musculature for relief of pain in osteoarthritis of the hip was introduced by Voss (1956). In his original operation he performed a fasciotomy of the iliobibial tract, a basal osteotomy of the greater trochanter, and a wide subcutaneous adductor tenotomy. This was quite an extensive procedure and O'Malley (1959) suggested that release of the iliopsoas muscle was a more important factor. Layani, Cordier, Garnier, Roeser, and Paquet (1959) injected 1% lignocaine into various sites of proposed muscle division and found that the greatest relief of pain occurred from injection around the iliopsoas. The trochanter is immediately raised 2 to 3 cm. by tension of the iliopsoas. The wound is closed with Redon suction drainage. If the adductors are tight subcutaneous tenotomy is performed.

After the operation the patient lies free in bed until the sutures are removed and is then allowed up and about. The postoperative radiograph shows the lesser trochanter freed and at a higher level. Very little is required in the way of physical treatment, and the average time spent in hospital is two and a half weeks.

Clinical Material

In this series osteotomy of the lesser trochanter was carried out on 50 patients. Forty-five—19 men and 26 women—attended for follow-up and review of their 48 operations. Their average age at the time of operation was 61 years, range 36 to 78. The time of follow-up was one to seven years, mean three and a half years.

Of the 48 hips 30 were thought to have primary or idiopathic osteoarthritis, 10 rheumatoid arthritis, and eight secondary osteoarthritis. To be classified as rheumatoid arthritis cases had to show radiographic changes in the hands as well as the hip, a raised erythrocyte sedimentation rate, and a positive latex fixation test.

Results

The results have been analysed in three groups, according to the aetiology. The results were assessed by considering relief of pain, functional activity, movement of the hip, and radiographic appearances.

Relief of pain.—Pain was the main reason for operation. The relief of pain has been classified into complete relief, partial relief, and no relief (Table I). Patients with complete relief were free from pain from the time of operation to follow-up. Those with partial relief were initially pain-free and then had recurrence; the average time of recurrence was one year after operation. In the two cases of rheumatoid arthritis pain recurred at 12 and 14 months; this pain was less than before operation and neither patient felt that further treatment was necessary.

| Table I |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Primary osteoarthritis | 15 | 8 | 2 | 0 |
| Rheumatoid arthritis | 14 | 2 | 0 | 0 |
| Secondary osteoarthritis | 3 | 3 | 2 | 0 |

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divided with a broad osteotome. The osteotome should be directed anteromedially so as to cut the lesser trochanter flush with the femur. The trochanter is immediately raised 2 to 3 cm. by tension of the iliopsoas. The wound is closed with Redon suction drainage. If the adductors are tight subcutaneous tenotomy is performed.

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Table I

<table>
<thead>
<tr>
<th>Condition</th>
<th>Complete Relief</th>
<th>Partial Relief</th>
<th>No Relief</th>
</tr>
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<tbody>
<tr>
<td>Primary osteoarthritis</td>
<td>15</td>
<td>8</td>
<td>2</td>
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<tr>
<td>Rheumatoid arthritis</td>
<td>14</td>
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<tr>
<td>Secondary osteoarthritis</td>
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