Sleep Studies with Clomipramine (Anafranil) and Related Drugs

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In recent years it has been realised that sleep is a time unusually convenient for making a variety of measures of human brain function. There is a relative freedom from the ever-varying environmental stimuli of waking life. One has the simple model of (a) a brain at rest with no drug (b) a brain with drug (c) the brain when the drug has been withdrawn.

My colleagues and I at Edinburgh are among those who have used techniques for studying some actions of anti-depressant drugs on electrophysiological features of sleep.

REM sleep deprivation
There are two principal kinds of sleep, usually known as NREM (non rapid eye movement, orthodox or slow wave) sleep and REM (rapid eye movement, paradoxical, desynchronized, 'dreaming') sleep. The former occupies about 77% and the latter about 23% of human sleep duration. Dement (1960) carried out selective deprivation of REM sleep in volunteers using behavioural techniques and noted that there was a subsequent 'compensatory' increase in the duration of REM sleep. At that time he equated the latter with dreaming and proposed that deprivation of dreams resulted in hallucinations and psychosis (Fisher & Dement 1963). It was an hypothesis that fired the imagination of newspaper and television script writers. However, a great many subsequent experimenters have failed to confirm the hypothesis. Deprivation of REM sleep certainly leads to a subsequent temporary increase of REM sleep above normal, but does not lead to psychosis or hallucinations.

MAOIs
There are many drugs that reduce the proportion of REM sleep in the whole night, and only a very few, such as reserpine (Hartmann 1966; Hoffman & Domino 1969) will increase REM sleep. A small group of drugs have an outstandingly powerful effect in suppressing REM sleep when used and these are all mood elevators, namely, dexamphetamine (Lewis 1970), the mono-amine oxidase inhibitors such as phenelzine (Akindele et al 1970, Wyatt et al 1971), and the tricyclic anti-depressants (Dunleavy et al 1972). In the case of the mono-amine oxidase inhibitors (MAOIs) there is a critical dose phenomenon, and only if a critical dose is exceeded does REM sleep suppression occur.

If it does occur it may not be apparent at all for the first week and sometimes two or three weeks are needed before all signs of paradoxical sleep are totally abolished and remain so for as long as the drug is given. In a recent study of 22 patients with endogenous depression, it was found that in those cases in whom mood response to the phenelzine occurred, the delay to the beginning of sustained mood elevation coincided with the delay between starting the drug and the abolition of the signs of REM sleep (Dunleavy & Oswald 1973). In the case of the MAOIs therefore, far from suppression of REM sleep being associated with the onset of psychosis,
it is associated with improvement from depression.

**Tricyclic drugs**

The tricyclic anti-depressant drugs nearly all cause suppression of REM sleep apparent within an hour or two of oral ingestion, indicating rapid absorption and entry into the brain (Dunleavy et al 1972). A dose of 75 mg of desipramine, for example, will cause suppression of REM sleep from the normal 23% down to about 5%, but this latter percentage will gradually rise again during the course of a month of continued administration. When the drug has been withdrawn a rebound occurs, having a duration of about a month. The same phenomenon is seen with a similar dose of imipramine, but the same dose of clomipramine is more powerful than any other tricyclic anti-depressant in having this effect on the brain, in that it causes an immediate abolition of paradoxical sleep. On withdrawal of clomipramine there is again a rebound with a duration of the same order as with desipramine or imipramine, indicating that the drugs induced changes in brain components having a life-span of weeks. This extremely powerful action of clomipramine has also been observed by Passouant et al. (1972). They, too, observed that there were sometimes brief episodes of an anomalous form of sleep in which there would be the EEG signs of REM sleep, together with some rapid eye movements, but with retention of fairly high muscle tension that is never seen in true REM sleep.

In our own experiments trimipramine had no effect on REM sleep. Clomipramine is particularly powerful in blocking 5-HT uptake mechanisms for mouse neurones and human platelets, whereas trimipramine is very weak. However, desimipramine has more of an effect in blocking noradrenaline uptake. One is driven to the conclusion that there is no simple relationship between the actions of tricyclic drugs on REM sleep, and the actions on brain amines that others have deduced from acute animal experiments (Dunleavy et al 1972).

Offermeier & Potgieter (1969) found that after MAOI pre-treatment, clomipramine caused a large increase in motility in mice. In our own studies we found that clomipramine caused increase in the frequency per unit time of shifts into stage 1 sleep (drowsiness) or wakefulness from any other stage of sleep. Whereas the effect on REM sleep changed slowly with time during the month of administration, this effect on the shifts (that may be termed intra-sleep restlessness) showed no change with time and no withdrawal rebound.

**Discussion**

Studies of tricyclic drug actions upon human brain are few because there are few easily measurable human brain functions. Electro-physiological techniques can, however, conveniently be applied during sleep, but the results of such studies will not at the present time tell us whether a drug is an effective anti-depressant or a clinically useful hypnotic. It has, however, told us that in one particular respect, clomipramine is, dose for dose, more powerful in its actions than any other tricyclic anti-depressant. It has also drawn our attention to the slowness of some changes wrought in the brain and that while some processes gradually change with time under the influence of a drug, (eg REM sleep duration), other functions do not change with time under the influence of the drug (eg intra-sleep restlessness). The long duration of the rebound following the withdrawal of such drugs as desipramine or clomipramine reminds us that when the brain has gradually been changed by anti-depressant drugs, the components so changed include some with a long life-span. It is known that among neuronal amine mechanisms are some in which components have life-spans of about a month (Häggendal & Dahlström 1969, Häggendal 1970). It is possible therefore that the therapeutic effects of tricyclic drugs such as clomipramine may proceed through the slow modification of cerebral components having life-spans of this order (Oswald et al 1972).

Mention has already been made of the curiously powerful effect of mood elevating drugs in suppressing REM sleep, and it is therefore intriguing to note that deliberate deprivation of REM sleep by behavioural techniques has been reported to cause elevation of mood in depressed patients (Vogel et al 1972). It must be left to other investigators to determine whether the uniquely
powerful immediate effect of clomipramine on REM sleep mechanisms may correlate with anti-depressant properties.

REFERENCES


Dunleavy D L F & Oswald I (1973) Phenelzine, mood response and sleep. *Archives of General Psychiatry* 28


