by Kempe *et al.* (1956) and Lewis and Johnson (1957), the deficiency being one of quality rather than quantity.

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Susceptibility to Methylpentynol and Methylpentynol Carbamate

Methylpentynol carbamate ("oblivon carbamate") has been used as an alternative to methylpentynol. Non-specific adverse effects have been recorded after a few daily oral doses of 1-2 g. of methylpentynol (May and Ebaugh, 1953; Marley and Chambers, 1956) and after larger (1-3 g.) and more protracted dosage (one to seven weeks) with methylpentynol carbamate (Bartholomew *et al.*, 1958). These last workers stressed that toxic abnormalities were unlikely if the daily oral dose of the carbamate did not exceed 1 g. It seemed important to ascertain whether this stricture held good for a population known to be especially sensitive to methylpentynol.

METHODS

Methylpentynol carbamate was administered to 10 subjects who had previously developed toxic phenomena while receiving a five-day therapeutic trial of 0.5 g. q.d.s. of methylpentynol, a baseline of individual reaction having been obtained by the immediate prior administration of inert capsules for five days. Similarly with the carbamate, inert tablets were prescribed for five days and were immediately succeeded by 0.2 g. q.d.s. of the active substance for the same period. A lapse of at least a month occurred between the two drug trials, and the patient received no other medication during either the placebo or the drug phase.

Their consent having been obtained, the subjects were informed that they would receive a drug from which they might or might not derive benefit. Each was interviewed daily, and if marked toxic features appeared the drug was withdrawn.

Toxic developments were graded into three categories. A maximal toxic reaction presented with pupillary abnormalities, nystagmus, diplopia, ptosis, dysarthria, and tremor of the outstretched tongue. A cerebellar type of ataxia might be found in the limbs or admixtures of this with a posterior-column type of ataxia and a positive Romberg sign. A minimal toxic reaction was epitomized by little more than nystagmus on conjugate lateral gaze and perhaps slight unsteadiness of gait or drowsiness. No reaction to the drug implied the absence of physical signs, although there might be a concomitant change of mood such as mild elation. The data obtained were analysed by means of an arc-sine transformation, a useful test of significance for small populations (Davies, 1954).

The series included five males and five females with an age range from 19 to 45 years, and minimal and maximal weights of 8 st. 6 lb. and 11 st. 13 lb. (53.52 and 75.75 kg.).

RESULTS

The distribution of patients allotted to the three clinical gradings for both drugs is depicted in the Table. This shows that there is a much smaller occurrence of toxic effects with methylpentynol carbamate than with methylpentynol. On analysis with the arc-sine transformation, the proportion of patients developing adverse features with methylpentynol (10/10) is found to be significantly greater

Distribution for Clinical Response to Methylpentynol and Methylpentynol Carbamate

Drug	Clinical Grading*		
	1	2	3
Methylpentynol	0	3	7
Methylpentynol carbamate	6	3	1

* Clinical grading: 3 = maximal toxic response; 2 = minimal toxic response; 1 = no toxic response.

than the proportion manifesting susceptibility to methylpentynol carbamate (4/10), the critical ratio being 3.96 ($P < 0.001$).

The time at which toxic phenomena with the two substances was first exhibited, and the number of subjects, are shown in the Chart; from this it can be seen that the maximum incidence was at the third day, although no instance occurred prior to this.

The details relating to the only subject showing a maximal toxic response to methylpentynol carbamate are as follows:

The patient was an unmarried woman weighing 9 st. 4 lb. (46.72 kg.) and aged 45. After five days of methylpentynol carbamate (0.2 g. q.d.s.), she had suffusion of the conjunctivae, sustained rhythmic nystagmus on conjugate lateral

Time and incidence of first appearance of toxic signs with methylpentynol and methylpentynol carbamate.

gaze, bilateral ptosis, sluggish reaction of the pupils to light, loss of tone in the facial musculature, dysarthria, and tremor of the outstretched tongue. There were cerebellar defects, including dysidiadokokinesis and ataxia on the finger-nose test in the upper limbs, with ataxia on the heel-shin test in the lower limbs. Her gait was ataxic, associated with a positive Romberg sign and overall reduction of the tendon reflexes. Her mental state was one of mild depression with impairment of attention and concentration, although orientation was correct. Within three days of stopping the drug the clinical abnormalities disappeared.

COMMENT

It is shown that, for the five-day period under scrutiny, methylpentynol carbamate is much superior to methylpentynol in its freedom from incidental toxicity. However, in a population known to be especially sensitive to methylpentynol, the use of the carbamate as an alternative in doses of 1 g. a day, or greater, is likely to be followed by the early manifestation of toxic signs.

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