Pharmacology Biochemistry & Behavior, Vol. 30, pp. 483–488. © Pergamon Press plc, 1988. Printed in the U.S.A. 0091-3057/88 $3.00 + .00

Sex Differences in Physical Dependence on Methaqualone in the Rat

T. SUZUKI, Y. KOIKE AND M. MISAWA

Department of Applied Pharmacology, School of Pharmacy
Hoshi University, Shinagawa-ku, Tokyo 142, Japan

Received 10 August 1987

SUZUKI, T., Y. KOIKE AND M. MISAWA. *Sex differences in physical dependence on methaqualone in the rat.* PHARMACOL BIOCHEM BEHAV 30(2)483–488, 1988.—The establishment of, and sex differences in, physical dependence on methaqualone (MQ) in rats were studied by the drug-admixed food (DAF) method. Female and male rats were treated with MQ-admixed food on the same schedule of gradually increasing doses (0.5 and 1 to 6 mg of methaqualone/g of food). Only female rats showed hypothermia from MQ at 1 and 2 mg/g and motor incoordination from MQ at 4 and 6 mg/g of food. Moreover, after MQ withdrawal, severe withdrawal signs, including convulsions and death, were observed in female rats, but not in male rats. We also instituted a different schedule of graded increases in dose (1 and 2 to 10 and 12 mg/g of food) to develop physical dependence on MQ in male rats. Under this schedule male rats exhibited a hypothermia and severe motor incoordination from MQ 6 and 8 mg/g of food condition. After MQ withdrawal, various severe signs of MQ withdrawal occurred, including tremor, convulsions and death. These results demonstrate that severe physical dependence on MQ in both sexes can be established using the DAF method, and that there are marked sex differences in the physical dependence on MQ.

Methaqualone Physical dependence Rat Sex difference Drug-admixed food method

METHAQUALONE, a quinazolone derivative, is a non-barbiturate sedative-hypnotic and anticonvulsant agent [6–8]. Its misuse by young people as a "pop up pill" has been reported by clinicians [27]. Ewart and Priest [4], Madden [14] and Kato *et al.* [11] reported that methaqualone caused physical dependence in man, while Martin [15] did not.

In laboratory animals (dogs [3,10], rats [13,21] and mice [1]), evidence for physical dependence on methaqualone has been reported. In barbital- or pentobarbital-dependent dogs, the degree of withdrawal signs after barbiturate withdrawal was lessened by methaqualone [3,10]. These reports suggest that methaqualone may possess cross-physical dependence liability with barbiturates. In rats kept on a semifluid diet that included methaqualone for 21 days, convulsions were produced by audiogenic stimuli after methaqualone withdrawal [13,21]. Moreover, the latencies of convulsion induced by flurothyl in methaqualone-treated mice were reduced after methaqualone withdrawal [1]. These authors used audiogenic stimuli or a chemical agent for evaluation of methaqualone withdrawal signs. However, severe physical dependence on methaqualone, as manifested by spontaneous convulsions after its withdrawal, has not been documented, suggesting that physical dependence on methaqualone is less frequent and of a milder type. Moreover, Yanagita and Miyasato [29] found that methaqualone does not produce any physical dependence in rhesus monkeys, but can function as a reinforcer for monkeys in an intravenous self-administration procedure.

In the previous report [22], we demonstrated that marked sex differences exist in the physical dependence on pentobarbital in rats. It is suggested that these sex differences may be due to sex differences in drug metabolizing enzyme activity. Furthermore, we demonstrated that weak sex differences in physical dependence on barbital, which is not readily metabolized in rats, exist [23], suggesting that these sex differences may result from a difference in CNS sensitivity to barbital. Nevertheless, sex differences in acute and chronic methaqualone effects have not yet been reported.

The purpose of the present study was to develop in rats severe physical dependence on methaqualone, characterized by spontaneous convulsions during withdrawal. In addition, sex differences in development of physical dependence on methaqualone were examined.

METHOD

Animals

Male and female Sprague-Dawley rats were used weighing about 160 and 140 g, respectively, at the beginning of exper-

TABLE 1

SCHEDULE OF PROGRESSIVELY INCREASED DOSES FOR DEVELOPMENT OF PHYSICAL DEPENDENCE ON METHAQUALONE IN EXPERIMENTS 1 AND 2

Experiment 1		Experiment 2	
Concentration (mg/g of food)	Duration (days)	Concentration (mg/g of food)	Duration (days)
1 and 2	3	0.5 and 1	5
2 and 4	3	1 and 2	5
4 and 6	3	2 and 4	7
6 and 8	4	4 and 6	10
8 and 10	10	6	10
10 and 12	10		

When rats were treated with one dose of methaqualone, there was one food container in a cage. And when rats were treated with two doses, there were two food containers in a cage.

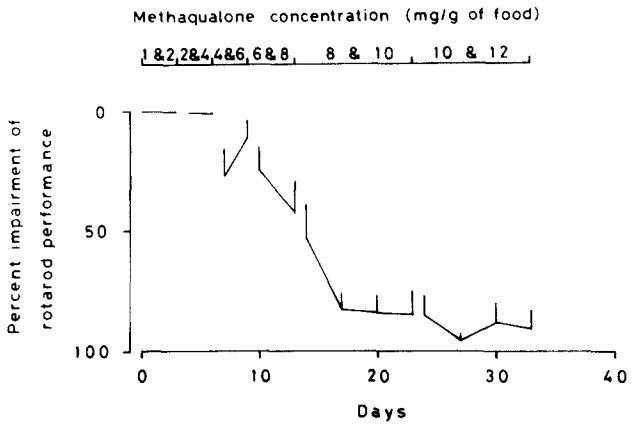

FIG.1. Rotarod performance during methaqualone-admixed food treatment in Experiment 1. Each point is a mean of 12 observations, and vertical lines indicate SEM.

iments. Hosoya [9] demonstrated young rats less than 100 g should not be used for the experiments, when rats were used as animal models of physical dependence. Animals were housed in individual cages under a 12-hr light-dark cycle with food and water continuously available. The room temperature and relative humidity were maintained at 22±1°C and 55±5%.

Drug Treatment

For preparing the drug-admixed food, methaqualone was mixed with a normal food powder (CA-1, Japan Clea, Tokyo, Japan) in a mortar [25, 30, 31]. Each rat was allowed to eat the methaqualone-admixed food and drink tap water ad lib. The concentration of methaqualone in the food was gradually increased in the course of day, as shown in Table 1. When rats were treated with one dose of methaqualone, there was one food container in a cage. When rats were treated with two doses (e.g., 0.5 and 1 mg/g of food), there were two food containers with each dose in a cage. During several phases of training rats were given simultaneous access to two concentrations of methaqualone in order to avoid or minimize toxicity of the drug. Body weight and food consumption were measured daily at 14:00. Daily methaqualone intake was calculated as follows:

$$\text{methaqualone intake (mg/kg/day)} = \frac{\text{food intake (g/day)} \times \text{concentration (mg/g of food)}}{\text{body weight (kg)}}$$

Measurements of Motor Incoordination and Rectal Temperature

Motor incoordination in methaqualone-treated rats was measured with a 5-min test on a rotarod performance apparatus (9 cm in diameter, 5.3 rpm; Natsume Seisakusho Co., Tokyo, Japan). Each rat was trained to run on a rotarod until it could remain there for 5 min without falling. Rectal temperature was measured by using a thermometer (3-A, 2087 type; Natsume Seisakusho Co., Tokyo, Japan). The temperature was recorded when a constant reading was obtained after rectal insertion of the probe (type PT, Shibaura Electronics Co., Ltd., Tokyo, Japan) to approximately 2.5 cm. The rotarod performance test and the measurement of rectal temperature were carried out at intervals of 1–4 days during methaqualone treatment.

Withdrawal

Withdrawal was conducted by substituting normal food for methaqualone-admixed food on the last day of the treatment at 14:00. Body weight and food intake were measured and withdrawal signs were observed every 3 hr after the termination of drug access. To quantify the intensity of physical dependence on methaqualone, a rating score for withdrawal signs was used. We classified the withdrawal signs into four grades, no abnormality (score 0), mild (score 1), intermediate (score 2) and severe (score 3). These grades of withdrawal signs were used according to the method of Tagashira *et al.* [25], with minor modifications.

Statistical Analysis

Analysis for the incidence of withdrawal signs was performed by the chi-square (2×2) test. All other analyses were carried out using the Student's *t*-test.

Experiment 1: Induction of Physical Dependence on Methaqualone

During the experiment, 17 male animals were divided into two groups: a methaqualone-treated group (n=12) and a control (non-treated) group (n=5). Furthermore, when methaqualone was withdrawn, methaqualone-treated rats were subdivided into two groups, a withdrawal group (n=6) and a dependent (non-withdrawal) group (n=6).

Experiment 2: Sex Differences in Physical Dependence on Methaqualone

During the experiment, male and female animals were each divided into two groups: a methaqualone-treated group and a control (non-treated) group. Furthermore, female methaqualone-treated rats were divided into two subgroups the same as Experiment 1.

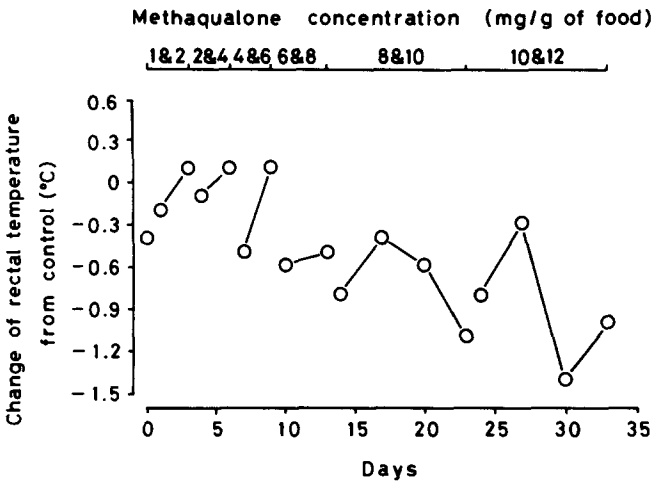

FIG. 2. Changes of rectal temperature from control during methaqualone-admixed food treatment in Experiment 1.

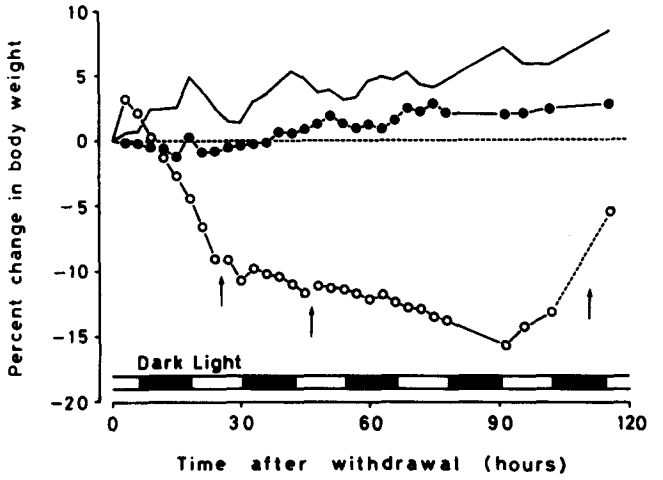

FIG. 3. Time course changes in body weight (%) after the termination of methaqualone treatment in Experiment 1. The arrows indicate that rats died at that time. Each point is a mean of 4 to 7 observations.

RESULTS

Experiment 1: Induction of Physical Dependence on Methaqualone

Relative to naive rats, body weight of methaqualone-treated rats decreased on the first day of 8 and 10 mg of methaqualone/g of food, and weight gain in methaqualone-treated rats was suppressed thereafter. The range of methaqualone intake was about 100 (at 1 and 2 mg/g of food) to 750 mg/kg/day (at 10 and 12 mg/g of food). The mean drug intake at the final methaqualone concentration (10 and 12 mg/g of food) was 731.3±17.4 mg/kg/day. Figure 1 presents changes in rotarod performance as a function of increases in methaqualone concentration. The rotarod performance was moderately affected at a drug concentration of 6 and 8 mg/g of food and decreased to 5% of control performance during treatment with 10 and 12 mg of methaqualone/g of food. Changes in rectal temperature of methaqualone-treated rats are shown as the differences between control and methaqualone-treated rats (Fig. 2). Hypothermia (a decrease of more than 0.3 °C) was observed on the first day of 4 and 6 mg of methaqualone/g of food, and then recovered on the last day of 4 and 6 mg of methaqualone/g of food condition. This result indicates that rats showed the tendency to develop tolerance to methaqualone. But, hypothermia was again observed when the methaqualone concentration was 6 and 8 mg of methaqualone/g of food or greater.

TABLE 2

BEHAVIORAL CHANGES AFTER THE TERMINATION OF METHAQUALONE TREATMENT IN EXPERIMENT 1

Withdrawal Signs (score)	Rats Exhibiting Withdrawal Signs/ Total Number of Animals (%)		
	Withdrawal Group	Dependent Control	Naive Control
Anorexia (1)	6/6 (100.0)	0/6‡ (0.0)	0/5‡ (0.0)
Vocalization (2)	3/6 (50.0)	0/6* (0.0)	0/5 (0.0)
Irritability (2)	1/6 (16.7)	0/6 (0.0)	0/5 (0.0)
Muscle rigidity (2)	6/6 (100.0)	0/6‡ (0.0)	0/5‡ (0.0)
Straub's tail (2)	6/6 (100.0)	0/6‡ (0.0)	0/5‡ (0.0)
Ear-twitching (2)	6/6 (100.0)	0/6‡ (0.0)	0/5‡ (0.0)
Fascicular-twitching (3)	6/6 (100.0)	0/6‡ (0.0)	0/5‡ (0.0)
Salivation (3)	4/6 (66.7)	0/6* (0.0)	0/5* (0.0)
Tremor (3)	5/6 (83.3)	0/6† (0.0)	0/5† (0.0)
Convulsion (3)	5/6 (83.3)	0/6† (0.0)	0/5† (0.0)
Death (3)	3/6 (50.0)	0/6* (0.0)	0/5 (0.0)
Withdrawal scores	19.3 ± 2.3	0 ± 0[a]	0 ± 0[a]

*$p<0.05$, †$p<0.01$, ‡$p<0.001$ vs. withdrawal group. The chi-square (2×2) test was used in the statistical evaluation for each withdrawal sign.

[a]$p<0.001$ vs. withdrawal group. Analysis for the withdrawal scores was performed by the Student's t-test. The withdrawal scores calculated by the sum of the rating score per animal.

After substituting normal food for methaqualone-admixed food, several signs of methaqualone withdrawal were observed (Table 2). These signs included vocalization, irritability, muscle rigidity, Straub's tail, ear-twitching, tremor and convulsions which are also the primary characteristics of the barbiturates withdrawal syndrome. Moreover, 3 out of 6 rats died due to convulsions and physical stress associated with withdrawal. Withdrawal scores in the withdrawal group, the dependent control and the naive control were 19.8±2.3, 0±0 and 0±0, respectively. The withdrawal scores in the withdrawal group was significantly greater than those in the dependent ($p<0.01$) and naive control ($p<0.01$). As shown in Fig. 3, body weight of animals treated with methaqualone increased immediately after methaqualone withdrawal and then decreased abruptly. The maximum percent weight loss in the withdrawal group was 15.65±8.19% at 91.5 hr after withdrawal. The dependent (non-withdrawal) group and the control group showed no decrease in body weight.

Experiment 2: Sex Differences in Physical Dependence on Methaqualone

The growth curves in male and female methaqualone-treated rats were suppressed as compared with respective controls under methaqualone concentrations of more than 2 and 4 mg/g of food. These suppressions were greater in male than in female rats. The range of methaqualone intake in

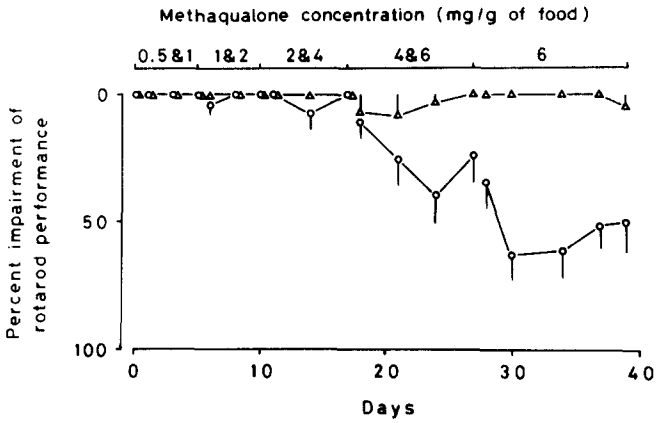

FIG. 4. Rotarod performance during methaqualone-admixed food treatment in Experiment 2. Each point is a mean of 6 to 7 observations, and vertical lines indicate SEM. ○: Female, △: Male.

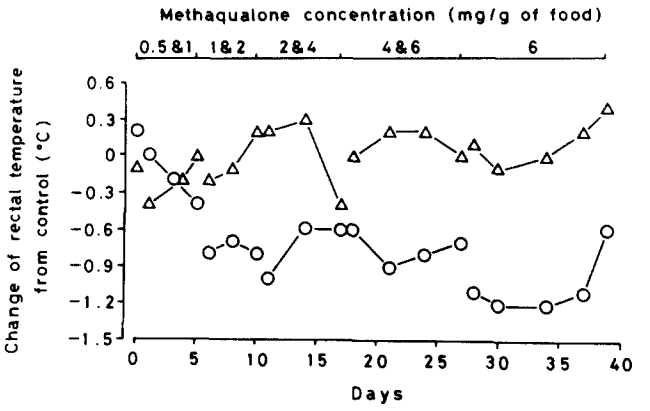

FIG. 5. Changes of rectal temperature from respective control during methaqualone-admixed food treatment in Experiment 2. ○: Female, △: Male.

both sexes was about 50–430 mg/kg/day (at 0.5 and 1 to 6 mg/g of food, respectively). The mean drug intakes during the final methaqualone concentration (6 mg/g of food) in male and female rats were 389.6±9.8 and 425.5±8.0 mg/kg/day, respectively. There was no significant difference in drug intake between male and female rats. Figure 4 shows changes in rotarod performance as a function of increases in methaqualone concentration from the 0.5 and 1 mg/g combination to 6 mg/g of food. The rotarod performance in female rats was affected at concentrations above 4 and 6 mg/g of food. More than 50 percent impairment of rotarod performance was seen at 6 mg/g of food. But impairment of rotarod performance in male rats was not observed throughout the methaqualone treatment. Hypothermia produced by methaqualone in female methaqualone-treated rats tended to begin on the first day of drug treatment. A hypothermia of more than 0.6°C was shown continuously starting at 1 and 2 mg of methaqualone/g of food (Fig. 5).

After substituting normal food for methaqualone-admixed food, several signs of methaqualone withdrawal in female rats were observed, which were similar to those seen in male rats in Experiment 1 (Table 3). These included severe withdrawal signs such as spontaneous convulsions. Only female rats (4/7) died due to convulsions and physical stress associated with withdrawal. On the other hand, withdrawal signs in male rats were limited to muscle rigidity, Straub's tail and ear-twitching. Withdrawal scores in the female withdrawal group was 17.6±3.1, and significantly greater than those in the female dependent control (0±0) and naive control (0±0). The withdrawal scores in male withdrawal group and naive control were 4.1±0.4 and 0±0, respectively, and there was a significant difference between them ($p<0.001$). The maximum percent weight losses in male and female rats were 3.13±1.12% and 10.35±1.41%, respectively (Fig. 6) and there was a significant difference between sexes ($p<0.01$).

DISCUSSION

Methaqualone abusers have found it hard to discontinue the drug after several weeks of steady use [2, 4, 5, 11, 20, 26]. Attempts to reduce dosage lead to anxiety and tremors similar to the "shakes" that occur in alcoholics. Headache, appetite loss, nausea and abdominal cramps are also common. Persons suddenly deprived of the drug after taking large doses for a few weeks may suffer a syndrome that resembles delirium tremens. Convulsive seizures have also occurred which are similar to those seen following sudden withdrawal of barbiturates in chronic abusers. Kohli *et al.* [13] reported that audiogenic seizure susceptibility in methaqualone-treated rats was increased after withdrawal, but spontaneous convulsions were not observed. In other reports [1, 3, 10], animals have not shown spontaneous withdrawal convulsions. The findings of the present study are consistent with clinical case reports in which withdrawal signs, such as spontaneous tremor and convulsions, were observed. Withdrawal convulsions have been used as the most important index for severe physical dependence on drugs of the barbiturate type. Thus, in the present study, severe physical dependence on methaqualone was established with the drug-admixed food method.

The magnitude of CNS depression was evaluated by the rotarod performance test and the measurement of rectal temperature. Even after the appearance of CNS depression, the concentration of methaqualone continued to be increased, since the rats did not show signs of toxicity, such as loss of body weight and a decrease in food consumption. During the phases of each concentration, there tend to be shown tolerance development to the hypothermic effect of methaqualone (Fig. 2). Suzuki *et al.* [24] reported that four inbred strains of rats developed tolerance of motor impairment to pentobarbital using the same method. In the present study, the tolerance of motor impairment to methaqualone was not showed. From these data, it is possible that the degree of tolerance to methaqualone may be weaker than pentobarbital. But, the development of tolerance by maintaining a constant level of drug administration is not clear and is under further study. The severity of physical dependence has been estimated by grading withdrawal reactions [18,28]. We have demonstrated the importance for the development of severe physical dependence on sedative-hypnotic drugs in rats of maintaining drug conditions for about 10 days that produce rotarod impairment [22]. One hundred percent of rats receiving pentobarbital that showed greater the 50% impairment of rotarod performance for approximately 10 days exhibited spontaneous convulsions upon withdrawal of the drug, thus demonstrating that they

TABLE 3

BEHAVIORAL CHANGES AFTER THE TERMINATION OF METHAQUALONE TREATMENT IN EXPERIMENT 2

	Rats Exhibiting Withdrawal Sign/Total Number of Animals (%)				
	Female			Male	
Withdrawal Signs (score)	Withdrawal Group	Dependent Control	Naive Control	Withdrawal Group	Naive Control
Anorexia (1)	7/7 (100.0)	0/6‡ (0.0)	0/6‡ (0.0)	7/7 (100.0)	0/6 (0.0)
Vocalization (2)	2/7 (28.6)	0/6 (0.0)	0/6 (0.0)	0/7 (0.0)	0/6 (0.0)
Muscle rigidity (2)	7/7 (100.0)	0/6‡ (0.0)	0/6‡ (0.0)	7/7 (100.0)	0/6 (0.0)
Straub's tail (2)	7/7 (100.0)	0/6‡ (0.0)	0/6‡ (0.0)	3/7* (42.9)	0/6 (0.0)
Ear-twitching (2)	6/7 (85.7)	0/6† (0.0)	0/6† (0.0)	1/7† (14.3)	0/6 (0.0)
Fascicular-twitch (3)	5/7 (71.4)	0/6† (0.0)	0/6† (0.0)	0/7† (0.0)	0/6 (0.0)
Salivation (3)	5/7 (71.4)	0/6† (0.0)	0/6† (0.0)	0/7† (0.0)	0/6 (0.0)
Tremor (3)	4/7 (57.1)	0/6* (0.0)	0/6* (0.0)	0/7* (0.0)	0/6 (0.0)
Convulsion (3)	4/7 (57.1)	0/6* (0.0)	0/6* (0.0)	0/7* (0.0)	0/6 (0.0)
Death (3)	4/7 (57.1)	0/6* (0.0)	0/6* (0.0)	0/7* (0.0)	0/6 (0.0)
Withdrawal scores	17.6 ± 3.1	0 ± 0[a]	0 ± 0[a]	4.1 ± 0.4[a]	0 ± 0[b]

*$p<0.05$, †$p<0.01$, ‡$p<0.001$ vs. female withdrawal group. $p<0.001$ vs. male withdrawal group. The chi-square (2×2) test was used in the statistical evaluation for each withdrawal signs.

[a]$p<0.01$ vs. female withdrawal group. [b]$p<0.001$ vs. male withdrawal group. Analysis for the withdrawal scores was performed by the Student's t-test. The withdrawal scores calculated by the sum of the rating score per animal.

were severely physically dependent on the barbiturate [22]. In the present study, the incidence of spontaneous methaqualone withdrawal convulsions in male rats was 83.3% (Table 2). Thus, we were able to show that severe physical dependence on methaqualone was easily developed by the drug-admixed food method.

Body weights of animals which were treated with methaqualone increased immediately after methaqualone withdrawal (Figs. 3, 6). The increase might have resulted from the rebound of suppression of weight gain in methaqualone-treated rats, relative to naive rats, prior to withdrawal. Actually, food intake increased immediately after the withdrawal of methaqualone.

The present experiments demonstrate marked sex differences in the development of physical dependence on methaqualone in rats. Both male and female rats were treated by the same drug dosage schedule (Table 1), The mean drug intake during the final methaqualone concentration (6 mg/g of food) in male rats was not significantly different from that in female rats. Motor incoordination and hypothermia in females were greater than in males. Moreover, after the termination of methaqualone treatment, several signs of methaqualone withdrawal were observed in female rats, but not in male rats. Only female rats showed the marked withdrawal signs, such as fascicular-twitch, tremor, convulsions and death.

Suzuki *et al.* [22,23] reported that there were sex differences in physical dependence on barbiturates (pentobarbital and barbital) in the rat. It was suggested that sex differences in physical dependence on barbiturates is mainly due to sex differences in drug metabolizing enzyme activity. In addition, it was demonstrated that there are sex differences in CNS sensitivity to barbiturates [23]. On the other hand, there have not been reports of sex differences in methaqualone effects. Prabhu *et al.* [19] reported a major role for the liver in detoxification of methaqualone in rats and mice. Nowak *et al.* [17] showed that most of the administered

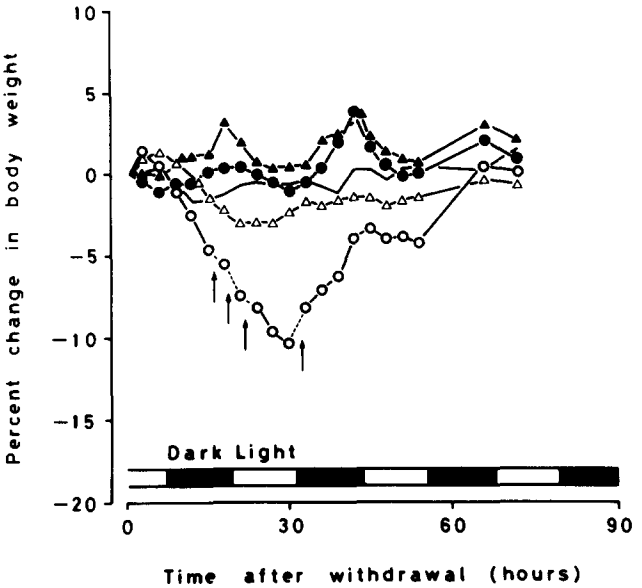

FIG. 6. Time course changes in body weight (%) after the termination of methaqualone treatment in Experiment 2. The arrows indicate that rats died at that time. ○: Female withdrawal group; −: Female naive group; ▲: Male naive group; ●: Female dependence group; △: Male withdrawal group.

methaqualone is hydroxylated in the body. Six different hydroxy derivatives were isolated from urine; almost all of them were glucuronides. The activities of hepatic microsomal drug-metabolizing enzymes are low in newborn and immature rats, and clear sex differences are not observed until 30 days of age [12]. The appearance of these differences in microsomal enzyme activities are coincident with the beginning of sex maturation (40 days of age) and the difference persists in normal adult rats until 600 days of age. Blood-brain barrier in rats was reported to develop until 2 weeks after birth [16]. These findings indicate that there may be sex differences in rate of methaqualone metabolism in rats. We thus suggest that the sex differences in physical dependence on methaqualone seem to be due to sex differences in drug metabolizing enzyme activity, as is the case with the barbiturates. These sex differences may be similar quantitatively or qualitatively in older rats (600 days of age). But, in addition, it is possible that sex differences in physical dependence on methaqualone may partly result from sex differences in CNS sensitivity and/or of development of tolerance to methaqualone.

ACKNOWLEDGEMENTS

We thank Drs. Richard A. Meisch and Gregory A. Lemaire for careful reading and criticism of the manuscript.

REFERENCES

1. Alpern, H. P., C. A. Greer, J. S. Stripling, A. C. Collins and R. K. Olson. Methaqualone: Tolerance and physical dependence in mice. *Psychopharmacologia* **44:** 303–305, 1975.
2. Coleman, J. B. and J. A. Barone. Abuse potential of methaqualone-diphenhydramine combination. *Am J Hosp Pharm* **38:** 160, 1981.
3. Deneau, G. A. and S. Weiss. A substitution technique for determining barbiturate-like physiological dependence capacity in the dog. *Pharmakopsychiatr Neuropsychopharmakol* **1:** 270–275, 1968.
4. Ewart, R. B. L. and R. G. Priest. Methaqualone addiction and delirium tremens. *Br Med J* **3:** 92–93, 1967.
5. González, E. R. Methaqualone abuse implicated in injuries, deaths nationwide. *JAMA* **246:** 813–819, 1981.
6. Gujral, M. L., P. N. Saxena and R. S. Tiwari. Comparative evaluation of quinazolones: A new class of hypnotics. *Ind J Med Res* **43:** 637–641, 1955.
7. Gujral, M. L., P. N. Saxena and R. S. Tiwari. Clinical evaluation of 2,3-disubstituted quinazolones for hypnotic effect. *Ind J Med Sci* **10:** 877–879, 1956.
8. Gujral, M. L., K. N. Sareen and R. P. Kohli. Evaluation of anticonvulsant activity of 2,3-disubstituted quinazolones: A new class of anticonvulsant drugs. *Ind J Med Res* **45:** 207–211, 1957.
9. Hosoya, E. Screening of dependence liability of drugs using rats. In: *Modern Pharmacology-Toxicology, Vol 5, Methods in Narcotics Research,* edited by S. Ehrenpreis and A. Neidle. New York: Marcel Dekker, 1975, pp. 261–291.
10. Jones, B. E., J. A. Prada and W. R. Martin. A method for bioassay of physical dependence on sedative drugs in dog. *Psychopharmacology (Berlin)* **47:** 7–15, 1976.
11. Kato, M., N. Takahashi, K. Miyagawa, K. Tauchi, E. Fujita, T. Suzuki and Y. Imada. Clinical and statistical study on drug dependence, in particular induced by tranquilizing and hypnotic drugs. *Clin Psychiatry* **8:** 119–128, 1966.
12. Kato, R. Sex-related differences in drug metabolism. *Drug Metab Rev* **3:** 1–32, 1974.
13. Kohli, R. P., N. Singh and V. K. Kulshrestha. An experimental investigation of dependence liability of methaqualone in rats. *Psychopharmacologia* **35:** 327–334, 1974.
14. Madden, J. S. Dependency on methaqualone hydrochloride (Melsedin). *Br Med J* **5488:** 676, 1966.
15. Martin, G. J. Dependency on methaqualone hydrochloride (Mersedin). *Br Med J* **5505:** 114, 1966.
16. Nomura, Y. Functional development of the synaptic transmission in the rat CNS and its interaction with drugs. *Folia Pharmacol (Japon)* **76:** 413–427, 1980.
17. Nowak, V. H., G. Schorre and R. Struller. Untersuchungen zum Metabolismus von Methaqualon. *Arzneimittelforschung* **16:** 407–411, 1966.
18. Okamoto, M., H. C. Rosenberg and N. R. Boisse. Tolerance characteristics produced during the maximally tolerable chronic pentobarbital dosing in the cat. *J Pharmacol Exp Ther* **192:** 555–569, 1975.
19. Prabhu, V. G., R. K. Browne and J. F. Zaroslinski. Studies on metabolism in rat and mouse of a new hypnotic-methaqualone. *Arch Int Pharmacodyn Ther* **148:** 228–236, 1964.
20. Rodman, M. J. Dangerous addictive: Abuse of methaqualone can be fatal. *RN: J Nurses* **36:** 70–72, 1973.
21. Singh, N., R. Nath, V. K. Kulshrestha and R. P. Kohli. An experimental evaluation of dependence liability of methaqualone diphenhydramine (combination) and methaqualone in rats. *Psychopharmacology (Berlin)* **67:** 203–207, 1980.
22. Suzuki, T., Y. Koike, T. Yoshii and S. Yanaura. Sex differences in the induction of physical dependence on pentobarbital in the rat. *Jpn J Pharmacol* **39:** 453–459, 1985.
23. Suzuki, T., Y. Koike, T. Yoshii and S. Yanaura. Sex differences in physical dependence on barbital in rats. *Jpn J Psychopharmacol* **6:** 373–380, 1986.
24. Suzuki, T., Y. Kioke, S. Yanaura, F. R. George and R. A. Meisch. Genetic differences in the development of physical dependence on pentobarbital in four inbred strains of rats. *Jpn J Pharmacol* **45:** 479–486, 1987.
25. Tagashira, E., T. Izumi and S. Yanaura. Experimental barbiturate dependence. I. Barbiturate dependence development in rats by drug-admixed food (DAF) method. *Psychopharmacology (Berlin)* **57:** 137–144, 1978.
26. Tennant, F. S. Complications of methaqualone-diphenhydramine (Mandrax®) abuse. *Br J Addict* **68:** 327–330, 1973.
27. Thacore, V. R., R. C. Saxena and R. Kumar. Epidemiology of drug-abuse with special reference to methaqualone. *Ind J Pharmacol* **3:** 58–65, 1971.
28. Yanagita, T. and S. Takahashi. Development of tolerance to and physical dependence on barbiturates in rhesus monkeys. *J Pharmacol Exp Ther* **172:** 163–169, 1970.
29. Yanagita, T. and K. Miyasato. Dependence potential of methaqualone tested in rhesus monkeys. *CIEA Preclin Rep* **2:** 63–68, 1976.
30. Yanaura, S., T. Suzuki and E. Tagashira. Study of drug dependence in rats—Substitution test and time course of body weight. *Folia Pharmacol (Japon)* **70:** 649–658, 1974.
31. Yanaura, S., E. Tagashira and T. Suzuki. Physical dependence on morphine, phenobarbital and diazepam in rats by drug-admixed food ingestion. *Jpn J Pharmacol* **25:** 453–463, 1975.