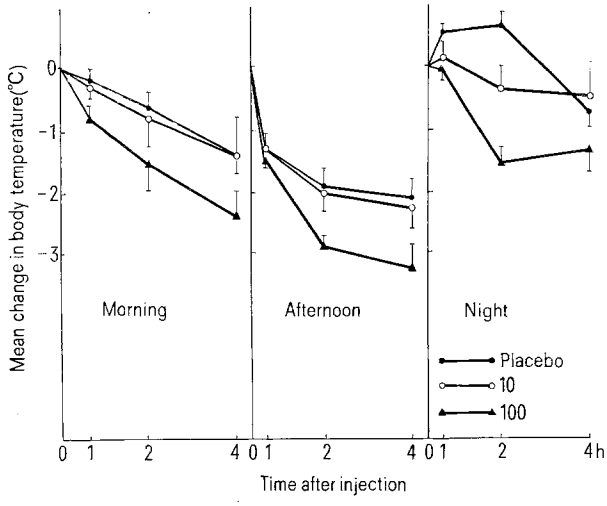
injections are made constitutes a significant variable in determining the magnitude of drug effect. The greatest degree of effect appears to occur when animals are injected during the afternoon, whereas the smallest changes in body temperature occur when injections are administered at night. The effects of the vehicle alone are likewise greatest and smallest at these times. There is also evidence of a slight increase in the body temperatures of the vehicle-treated animals during the first 2 h after injection in the latter group. Thus, at 4 h after treatment, the body temperatures of the control animals had decreased by −1.4, −2.1 and −0.6 °C for the morning, afternoon and night treatments repectively. The changes for the 10.0 mg/kg groups was −1.4, −2.2 and −0.4 °C and for the 100.0 mg/kg groups, these were −2.4, −3.2 and −1.3 °C respectively.

Thus, these data further illustrate the importance of the chronological variable in drug-related research. Methodologically, they suggest that drug-produced effects ought not to be compared when animals are tested or injected at different times of day, especially when subtle differences are expected.

With respect to the present experiment, the most likely explanation for the data is that since mice tend to be more active during the night and least active during the afternoon, this diurnal activity pattern most likely contributed to the overall effect by increasing motor activity at night and thus masking to some extent, the well known sedative-like effects of high doses of marihuana and its derivatives in animals (e.g., CARLINI, SANTOS, CLAUSSEN et al.[5]).



Changes in body temperature of mice treated at different chronological time periods. Vertical lines indicate the standard errors of the mean. There were 9 animals in each drug group.

Résumé. La température rectale de souris ayant subi une unique injection de Δ^9THC (injection administrée soit le matin, soit l'après-midi, ou soit durant la nuit) a été mesurée 1, 2 et 4 h suivant cette injection. Chez les animaux, injectés l'après-midi, l'abaissement de température était maximal, mais il fut minimal chez les animaux injectés de nuit.

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12 June 1973.

[5] E. A. CARLINI, M. SANTOS, U. CLAUSSEN, D. BIENIK and F. KORTE, Psychopharmacologia *18*, 82 (1970).

[6] Present address: Research Institute on Alcoholism, New York State Department of Mental Hygiene, 1021 Main Street, Buffalo (New York 14203, USA).

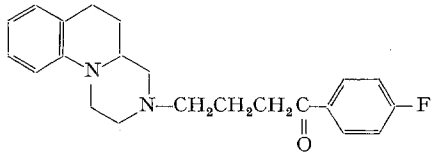
Antihypertensive and Central Nervous System Depressant Properties of 3-(γ-*p*-Fluorobenzoyl Propyl) 2,3,4,4a,5,6-hexahydro-1(H)-Pyrazino(1,2-a) Quinoline Hydrochloride (Compound 69-183, Centpyraquin)

Synthesis and preliminary pharmacological results of a series of quinoline derivatives have been reported earlier[1]. Centpyraquin (3-(γ-*p*-fluorobenzoyl propyl) 2, 3, 4, 4a, 5, 6-hexahydro-1(H)-pyrazino (1, 2-a) quinoline hydrochloride (compound 69-183, I) showed significant hypotensive and CNS depressant properties and a brief report of the important results is being presented.

Cardiovascular and autonomic effects in normotensive cats and dogs. Centpyraquin lowered the blood pressure of anaesthetized or immobilized (D-tubocurarine) cats and dogs. The minimum effective dose was 0.1 mg/kg i.v. which lowered the blood pressure by 10% for about 10 min. A dose of 1.0 mg/kg i.v. lowered the blood pressure by 47% for about 90 min. The response was still more marked with higher doses. Hypotension was accompanied by blockade of the nictitating membrane contraction due to both pre- and post-ganglionic stimulation, potentiation of the adrenaline and noradrenaline pressor responses and blockade of the tyramine pressor response. It had a positive inotropic effect in open chest, anaesthetised cats (upto 5 mg/kg i.v.) and in isolated perfused guinea-pig and rabbit hearts (100–200 μg).

Effect in hypertensive rats. Centpyraquin (10 mg/kg i.p. or oral) lowered the blood pressure of renal hypertensive rats by 20% for more than $3^1/_2$ h. With 20.0 mg/kg (i.p.), blood pressure was reduced by about 40% for 4 h. Daily administration (20 mg/kg i.p., once a day for 10 days) lowered the blood pressure by 30% and it returned to original level 3 days after the stoppage of the compound.

CNS effects in mice. The compound depressed the spontaneous motor activity of mice in doses of 30 mg/kg and above. Ptosis was a marked feature. Rectal tem-



Centpyraquin (I)

[1] V. A. RAO, P. C. JAIN, N. ANAND, R. C. SRIMAL and P. R. DUA, J. med. Chem. *13*, 516 (1970).

[2] L. COOK and E. WEIDLEY, Ann. N. Y. Acad. Sci. *66*, 740 (1957).

[3] Thanks are due to Drs. M. L. DHAR and N. ANAND for their interest in the work.

[4] Communication No. 1600 from the Central Drug Research Institute; Lucknow.

perature of the mice was reduced by 3.5 °C at a dose of 30 mg/kg i.p. The ED_{50} of the compound in rota rod test was 70.0 mg/kg. The compound significantly increased the duration of hexobarbitone, pentobarbitone and ethanol hypnosis. Amphetamine-induced hyperactivity (5 mg/kg), as well as group toxicity (40 mg/kg), was also antagonized. The ED_{50} of centpyraquin in the later test was 18.0 mg/kg i.p.

Blockade of conditioned avoidance (CAR) and unconditioned response (UCR) in rats. The ED_{50} for blockade of CAR and UCR were 2.5 and 10.0 mg/kg i.p. respectively in rats trained by the method of COOK and WEIDLEY[2].

Behavioural effect in monkeys and cats. Centpyraquin (5–10 mg/kg i.p.) had a marked taming effect on rhesus monkeys and cats. The animals became quiet and less agressive. There was marked ptosis in monkeys and relaxation of nictitating membrane in cats.

It can be concluded that centpyraquin possesses potent antihypertensive and CNS depressant properties. The site of the hypotensive action appears to be peripheral, possibly at adrenergic neurones, since the compound blocks the contraction of the nictitating membrane due to pre- as well as post-ganglionic sympathetic nerve stimulation and tyramine pressor response, while adrenaline and noradrenaline pressor responses are potentiated. In addition, it produces ptosis in mice, rats, monkeys etc. The CNS depressant properties resemble those of a major tranquillizer.

Zusammenfassung. Centpyraquin (3-(γ-*p*-fluorobenzyl propyl) 2,3,4,4a,5,6-hexahydro-1(H)-pyrazino (1,2-a) quinoline hydrochloride) zeigte hypotensive Aktivität bei narkotisierten wie auch bei wachen Katzen. Es senkt auch den Blutdruck bei Ratten mit nephrogenem Hochdruck. Die Hypotension scheint auf einem peripheren Mechanismus zu beruhen.

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Modifications du métabolisme de la dopamine cérébrale provoquées par l'injection intrapéritonéale d'une forte dose d'histamine chez le rat

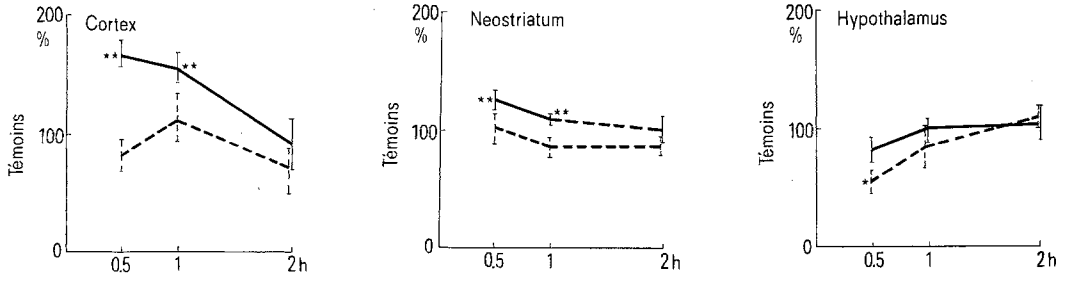
Lorsqu'elle est administrée à forte dose par voie intrapéritonéale chez le rat, l'histamine diffuse dans le système nerveux central[1] et développe des effets caractéristiques: catalepsie et potentialisation des stéréotypies induites soit par l'apomorphine, soit par la dexamphétamine[2]. Ces effets pouvant mettre en jeu des mécanismes dopaminergiques, nous avons recherché si, au cours de leur développement, le métabolisme de la dopamine cérébrale était modifié.

Protocoles expérimentaux. Le chlorhydrate d'histamine est injecté en solution aqueuse, à la dose de 400 mg/kg par voie intrapéritonéale (volume d'injection: 1 ml/100 g de poids corporel) à des rats (Wistar) de 4 semaines pesant 80 ± 10 g, les animaux témoins recevant dans les mêmes conditions, une injection de solution isotonique de NaCl (9 g/1000; p/v).

Les animaux sont sacrifiés par décapitation, 30, 60 et 120 min après l'injection (20 rats pour chaque temps). Les cerveaux sont immédiatement prélevés, disséqués selon la méthode de GLOWINSKI et IVERSEN[3]. Toutes les fractions obtenues, cervelet, neostriatum, cortex, hippocampe, hypothalamus, thalamus et tronc cérébral, sont groupés par deux. Dans chaque tissu, on dose la dopamine par la méthode de HINESLEY et al.[4] et l'acide homovanillique par la méthode de ANDEN et al.[5].

Résultats. Après injection d'histamine, on n'observe de variations significatives qu'au niveau de trois structures cérébrales, le cortex, le neostriatum et l'hypothalamus. Les résultats obtenus sont indiqués sur la figure. 30 min et 1 h après injection d'histamine, les concentrations de dopamine augmentent dans le cortex et le neostriatum alors que, parallèlement, les concentrations

[1] J. R. BOISSIER, J. P. TILLEMENT, M. GUERNET, A. NORTH-DIEHL et J. WINICKI, J. Pharmac., Paris *3*, 355 (1972).
[2] J. R. BOISSIER, Actual. pharmac. *24*, 51 (1971).
[3] J. GLOWINSKI et L. L. IVERSEN, J. Neurochem. *13*, 655 (1966).
[4] R. K. HINESLEY, J. A. NORTON et M. H. APRISON, J. Psychiat. Res. *6*, 143 (1968).
[5] N. E. ANDÉN, B. E. ROOS et B. WERDINIUS, Life Sci. *3*, 149 (1964).



Variations, en fonction du temps, des concentrations de dopamine et d'acide homovanillique dans le cortex, le neostriatum et l'hypothalamus de rat, après injection intrapéritonéale de chlorhydrate d'histamine (400 mg/kg). Les résultats sont indiqués en % (± 2 Sm) des témoins. Les variations de la dopamine sont figurées en traits pleins, celles de l'acide homovanillique en pointillé. Les variations significatives par rapport aux témoins sont indiquées respectivement par xx ($p < 0{,}001$) et par x ($p < 0{,}01$). Les concentrations observées chez les animaux témoins sont de (M ± Sm en ng/g de tissu frais):

	Cortex	Neostriatum	Hypothalamus
Dopamine	219,1 ± 9,6	5079,6 ± 87,0	376,0 ± 23,0
Acide homovanillique	7,5 ± 0,5	746,6 ± 26,9	55,4 ± 1,9