Kontraktionsamplitude, der Frequenz und der Noradrenalin-Abgabe traten hierbei schon in den ersten 2 min auf und fielen während der Infusion ab. In 3 Versuchen stieg die Kontraktionsamplitude maximal um 37 ± 7%, die Frequenz um 54 ± 15% und der Durchfluss sank um 28 ± 2%. Figur 1 zeigt, dass die Noradrenalin-Abgabe durch DMPP auf die ersten 2 min beschränkt ist, wobei etwa so viel Noradrenalin abgegeben wird (610 ± 69 µg), wie durch die 15 min dauernde Tyramin-Infusion (515 ng ± 40 ng). Die Tyramin-Konzentration von 5 µg/ml bewirkt bereits eine für diese Substanz maximale Noradrenalin-Freisetzung[10]. Eine Erklärung dafür, dass DMPP und Acetylcholin[8] nur zu Beginn ihrer Einwirkung Noradrenalin freisetzen, könnten elektrophysiologische

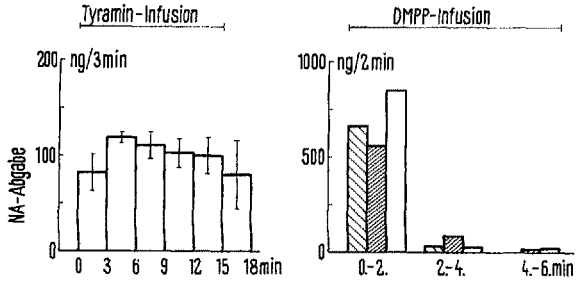


Fig. 1. Zeitlicher Verlauf der Abgabe von Noradrenalin (NA) aus dem perfundierten Kaninchenherzen während einer kontinuierlichen Tyramin- bzw. DMPP-Infusion. Tyramin 5 µg/ml, Mittelwerte aus 3 Versuchen ± $s_{\bar{x}}$. DMPP 3 Einzelversuche, 10 µg/ml (grob und fein schraffierte Säulen), 20 µg/ml (offene Säule). Ruheabgabe von NA 2,2 ng/min. Einzelheiten siehe Text.

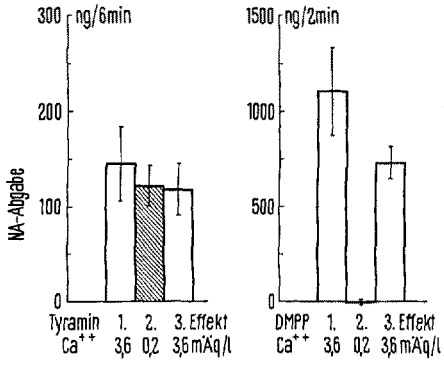


Fig. 2. Abgabe von Noradrenalin (NA) durch Tyramin- bzw. DMPP-Infusion bei verminderter $Ca^{++}$-Konzentration. Tyramin 5 µg/ml, DMPP 20 µg/ml, Mittelwerte aus 3 Versuchen ± $s_{\bar{x}}$. Einzelheiten siehe Text.

Befunde vom Ganglion cervicale superius der Katze bieten[11], wonach nikotinartig wirkende Substanzen eine initiale, nur kurz dauernde Depolarisation verursachten.

In einer Reihe weiterer Versuche wurde die $Ca^{++}$-Abhängigkeit der Noradrenalin-Freisetzung durch Tyramin und DMPP geprüft. Tyramin (5 µg/ml) bzw. DMPP (20 µg/ml) wurden in 3 aufeinanderfolgenden Effekten der Tyrodelösung zugesetzt, Tyramin für jeweils 6 min, DMPP für 2 min. Nach dem ersten Effekt wurde der $Ca^{++}$-Gehalt der Tyrodelösung von 3,6 auf 0,2 mÄq/l herabgesetzt und nach dem 2. Effekt wieder auf den Ausgangswert erhöht. Nach Veränderung des $Ca^{++}$ Gehalts wurde stets 15 min bis zum Beginn des nächsten Effekts gewartet. Wegen des verminderten $Ca^{++}$-Gehalts kontrahierten sich von 6 Herzen 2 nicht mehr, während es bei 4 Herzen zu einer Abnahme der Kontraktionsamplitude um 89 ± 4% und der Frequenz um 14 ± 8% kam. Der Durchfluss veränderte sich nicht signifikant. Figur 2 zeigt, dass die Noradrenalin-Abgabe durch Tyramin während einer Periode mit stark vermindertem $Ca^{++}$-Gehalt (2. Effekt) gegenüber der Noradrenalin-Abgabe bei unverändertem $Ca^{++}$-Gehalt (1. und 3. Effekt) nicht herabgesetzt ist. Dagegen ist die Noradrenalin-Abgabe durch DMPP bei vermindertem $Ca^{++}$-Gehalt vollständig gehemmt.

Im Gegensatz zur Wirkung von Tyramin ist die von DMPP ebenso an die Anwesenheit von $Ca^{++}$ geknüpft, wie dies früher für den Effekt von Acetylcholin[8] und sympathischer Nervenreizung[12] gezeigt wurde. Für den Bereich der sympathischen Nervenfaser fügen sich diese Befunde gut in die eingangs erwähnten Vorstellungen über den Mechanismus nikotinartiger und indirekt sympathomimetisch wirkender Substanzen ein.

*Summary.* On the perfused rabbit heart a constant infusion of tyramine released noradrenaline continuously and independently of the external $Ca^{++}$ concentration. In contrast, noradrenaline release by DMPP was only transient and required the presence of $Ca^{++}$.

R. LINDMAR, K. LÖFFELHOLZ und E. MUSCHOLL

*Pharmakologisches Institut der Universität Mainz (Deutschland), 5. Juni 1967.*

[10] R. LINDMAR, E. MUSCHOLL und E. SPRENGER, Arch. Pharmak. exp. Path. *256*, 1 (1967).

[11] C. TAKESHIGE und R. L. VOLLE, Br. J. Pharmac. Chemother. *23*, 80 (1964).

[12] S. HUKOVIC und E. MUSCHOLL, Arch. exp. Path. Pharmak. *244*, 81 (1962).

## Plasma Levels and Renal Excretion of Unchanged Methopholine[1] in Man

Recent pharmacological studies by BESENDORF et al.[2] and by BROSSI et al.[3] on a new synthetic analgesic[2] with a papaverine structure, 1-(*p*-chlorophenethyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroxoquinoline (= methopholine), showed the efficacy of its analgesic and spasmolytic action, devoid of the typical phenomena of addiction[4,5] of natural alkaloids. Information on the pharmacokinetics of methopholine in man is, however, scanty. No extensive data are available on the plasmatic and urinary levels of the drug, although a few data on its excretion and metabolites in man and rabbit have been reported[6,7]. Here the results are reported of determinations of plasma and urinary contents evaluated in man after administration of methopholine.

*Material and methods.* Sixteen apparently healthy volunteers (age 20–50) were used in this investigation, with three modes of administration: treatment A, a

single oral dose of 120 mg; treatment B, 3 oral doses of 120 mg each (total 360 mg) at 4 h intervals; treatment C, 360 mg daily in three 120 mg oral doses at 8 h intervals for 3 weeks.

*Chemical determination.* Unchanged methopholine in plasma and urine was determined by the spectrofluorometric method of SCHWARTZ et al.[6,7]. The addition of known amounts of methopholine (from 0.25–4.0 μg) to plasma and urine indicated recoveries ranging from 93% to 102% for plasma and 104% to 110% for urine.

*Results and discussion.* As shown in Figure 1 and in Tables I(A) and II(A), the single oral dose of 120 mg of methopholine quickly caused its appearance in the plasma, attaining a peak in about 80 min. Maximal concentrations between 0.24 and 0.42 μg/ml were found. Some unchanged methopholine remained in the body for a long time, since its excretion was rather slow (only 5‰ of the administered dose in 4 days). According to SCHWARTZ et al.[7], however, the drug is excreted mainly as conjugated metabolites. Figure 2 and Tables I(B) and II(B), concerning treatment B, show that the methopholine plasma content closely followed the pattern of administration: after the high initial rise (0.39 μg/ml)

[1] Methopholine is the proposed generic name for the active substance of the preparation 'Versidyne'.

[2] H. BESENDORF, B. PELLMONT, H. P. BÄCHTOLD, K. REBER and F. STUDER, Experientia *18*, 446 (1962).
[3] A. BROSSI, H. BESENDORF, B. PELLMONT, M. WALTER and O. SCHNEIDER, Helv. chim. Acta *43*, 1459 (1960).
[4] H. F. FRASER, W. R. MARTIN, A. B. WOLBACH and H. ISBELL, Clin. Pharmac. Ther. *2*, 287 (1961).
[5] H. F. FRASER, W. R. MARTIN, A. B. WOLBACH and H. ISBELL, Fedn Proc. Fedn Am. Socs exp. Biol. *20*, 310 (1961).
[6] D. E. SCHWARTZ and J. RIEDER, personal communication.
[7] D. E. SCHWARTZ, H. BRUDERER, J. RIEDER and A. BROSSI, Biochem. Pharmac. *13*, 777 (1964).

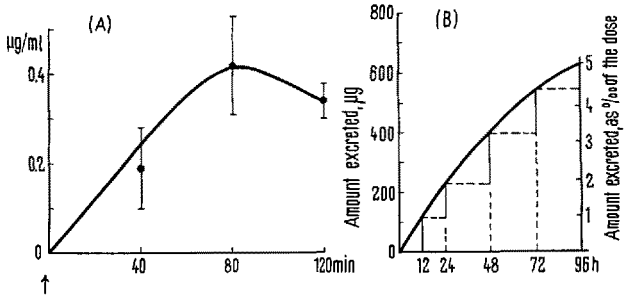


Fig. 1. (A) plasma content (μg/ml) and (B) urinary excretion (μg) of methopholine after a single oral 120 mg dose. Each value represents the mean of determinations on 4 subjects. ↑, administration; •, standard error.

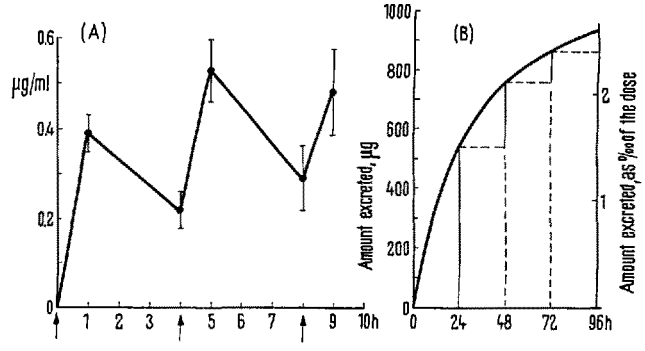


Fig. 2. (A) plasma content (μg/ml) and (B) urinary excretion (μg) of methopholine after oral administration of three 120 mg doses at 4 h intervals. Each value represents the mean of determinations on 6 subjects. ↑, administration; •, standard error.

Table I. Plasma content (μg/ml) of methopholine

| Treatment | Subjects | Time from administration | | | | |
|---|---|---|---|---|---|---|
| | | 40 min | | 80 min | | 120 min |
| (A) | 1 | 0.41 | | 0.43 | | 0.34 |
| | 2 | 0.02 | | 0.25 | | 0.25 |
| | 3 | 0.27 | | 0.26 | | 0.30 |
| | 4 | 0.08 | | 0.71 | | 0.46 |
| | Mean ± S.E. | 0.19 ± 0.09 | | 0.42 ± 0.11 | | 0.34 ± 0.04 |
| (B) | | 1 h | 4 h | 5 h | 8 h | 9 h |
| | 1 | 0.26 | 0.13 | 0.47 | 0.17 | 0.32 |
| | 2 | 0.47 | 0.27 | 0.83 | 0.33 | 0.51 |
| | 3 | 0.26 | 0.22 | 0.35 | 0.43 | 0.55 |
| | 4 | 0.45 | 0.39 | 0.44 | 0.52 | 0.42 |
| | 5 | 0.40 | 0.12 | 0.55 | 0.13 | 0.60 |
| | 6 | 0.51 | 0.20 | 0.52 | 0.15 | 0.49 |
| | Mean ± S.E. | 0.39 ± 0.04 | 0.22 ± 0.04 | 0.53 ± 0.07 | 0.29 ± 0.07 | 0.48 ± 0.10 |
| (C) | | 8th day | | 16th day | | 24th day |
| | 1 | 0.42 | | 0.30 | | 0.25 |
| | 2 | 0.22 | | 0.33 | | – |
| | 3 | 0.28 | | 0.18 | | 0.38 |
| | 4 | 0.20 | | 0.16 | | 0.26 |
| | 5 | 0.09 | | 0.32 | | 0.53 |
| | 6 | 0.07 | | 0.39 | | 0.53 |
| | Mean ± S.E. | 0.21 ± 0.04 | | 0.28 ± 0.04 | | 0.39 ± 0.06 |

(A) Single oral 120 mg dose; (B) three 120 mg daily doses at 4 h intervals; (C) three 120 mg daily doses, for 3 weeks.

Table II. Urinary excretion ($\mu$g) of methopholine

| Treatment | Subjects | Urine content of | | | | |
|---|---|---|---|---|---|---|
| | | 0–12 h | 12–24 h | 24–48 h | 48–72 h | 72–96 h |
| (A) | 1 | 75.3 | 88.2 | 66.9 | 253.0 | 33.0 |
| | 2 | 179.5 | 163.1 | 243.0 | 78.6 | 117.1 |
| | 3 | 105.0 | 81.2 | 178.0 | 148.0 | 102.1 |
| | 4 | – | – | – | – | – |
| | Mean ± S.E. | 119.9 ± 31.0 | 110.8 ± 26.2 | 162.6 ± 51.4 | 159.9 ± 50.7 | 84.1 ± 25.91 |
| | | 0–24 h | 24–48 h | 48–72 h | 72–96 h | |
| (B) | 1 | 900 | 288 | 115 | 171 | |
| | 2 | 814 | 320 | 150 | 161 | |
| | 3 | 546 | 356 | 162 | 24 | |
| | 4 | 329 | 86 | 27 | 27 | |
| | 5 | 270 | 72 | 28 | 59 | |
| | 6 | 386 | 220 | 117 | 42 | |
| | Mean ± S.E. | 541 ± 107 | 224 ± 49 | 100 ± 24 | 81 ± 27 | |
| | | 7th day | | 15th day | | 23th day |
| (C) | 1 | 1105 | | 1656 | | 820 |
| | 2 | 2532 | | 414 | | – |
| | 3 | 1330 | | 848 | | 1320 |
| | 4 | 729 | | 1781 | | 1703 |
| | 5 | 3997 | | 3185 | | 4830 |
| | 6 | 1775 | | 2328 | | 3660 |
| | Mean ± S.E. | 1911 ± 487 | | 1702 ± 407 | | 2467 ± 762 |

(A) Single oral 120 mg dose; (B) three 120 mg daily doses at 4 h intervals; (C) three 120 mg daily doses, for 3 weeks.

there followed a decrease (0.22 $\mu$g/ml) at the fourth hour, the highest value occurring after the second and third doses. Therefore the unchanged methopholine showed a slight initial accumulation in the plasma, as was to be expected because of the short time intervals between each administration. The daily urinary excretion of methopholine was highest in the first 24 h; then the daily increment did not greatly differ from that observed after a single dose. The total excretion of unchanged methopholine, following the application of 3 doses of 120 mg each, roughly doubled the amount excreted after the single dose, when expressed in microgrammes, but only halved the latter when expressed in ‰ of the dose. Possibly, the repeated dosage caused a higher amount of the drug to be metabolized to compounds likewise excreted in the urine[6,7]. In the chronic administration (treatment C), a total amount of 8.9 g of methopholine was administered. The interpretation of the results obtained (Figure 3, and Tables I(C) and II(C)) is restricted by the fact that only 3 determinations of the plasma content could be made in each patient just before the first daily administration. The concentration (0.21 to 0.39 $\mu$g/ml) did not differ from that found after the other 2 treatments. The rise of the content shown in Figure 3 might suggest a slight accumulation of the unchanged drug in the plasma during the first 3 weeks. However, the 3 values of Figure 3 are not statistically different from each other and fall in the concentration range found after a single dose of 120 mg. In conclusion, the plasma content of the unchanged methopholine remained constantly low and did not change markedly during the 3 weeks' experiment. If the efficacy of the drug depends on its plasma content, such a relative constancy of the concentration argues well for the persistence of the pharmacological effects of the analgesic. The daily urinary excretion of unchanged methopholine also remained fairly constant and moderate in treatment C. This moderate excretion is in accordance with the findings of SCHWARTZ et al.[7] that methopholine is rapidly and extensively metabolized.

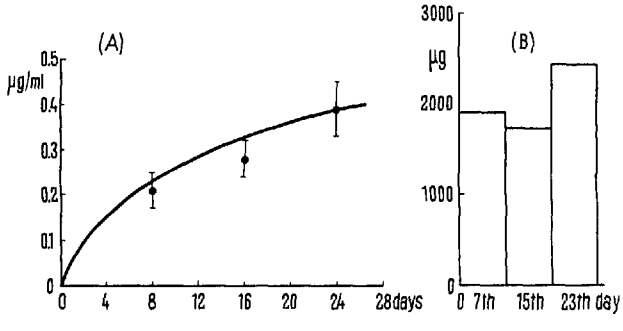


Fig. 3. (A) plasma content ($\mu$g/ml) and (B) urinary excretion ($\mu$g) of methopholine after oral administration of three 120 mg daily doses for 3 weeks. Each value represents the mean of determinations on 6 subjects. •, standard error.

*Riassunto.* I livelli plasmatici e l'eliminazione urinaria del methopholine immodificato sono molto bassi nell'uomo, in confronto alle varie dosi orali somministrate. Anche il trattamento trisettimanale non ha causato concentrazioni plasmatiche diverse da quelle ottenute con somministrazione singola o ripetuta. La sostanza è ampiamente trasformata nell'organismo ed escreta sotto forma di metaboliti vari.

G. SCIORELLI

*Istituto di Fisiologia umana, Università di Pavia, Pavia (Italy), 16th May 1967.*