Sedative and cardiovascular effects of medetomidine, a novel selective α_2 -adrenoceptor agonist, in healthy volunteers

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1 Single intravenous doses (25, 50 and 100 μ g) of medetomidine (MPV-785, an imidazole derivative), a selective α_2 -adrenoceptor agonist, were administered to eight healthy male volunteers in a double-blind, placebo-controlled study.

2 The following dose-related effects, all of which were compatible with an agonistic action of the drug at α_2 -adrenoceptors, were noted: reductions of systolic and diastolic blood pressure (maximum 18/11 mm Hg), heart rate (maximum 10 beats min^{-1}), saliva secretion (maximum 84%) and noradrenaline levels in plasma (maximum 70%).

3 Dose-dependent sedation or impairment of vigilance was also observed, both by subjective and objective (critical flicker fusion threshold) assessments, with the highest dose actually inducing sleep in five of the subjects.

4 The observed effects were in general agreement with those previously seen after intravenous administration of the centrally acting antihypertensive α_2 -adrenoceptor activating drug, clonidine, but of a shorter duration.

5 The relative importance of α_2 -adrenoceptors located in peripheral tissues and in the central nervous system for the drug's cardiovascular effects could not be determined, but the high lipid solubility of the compound and the rapid onset of sedation are in favour of a major central component.

6 Medetomidine may be a useful tool for the investigation of the physiology and pharmacology of α_2 -adrenoceptors in man. In addition, the therapeutic and diagnostic uses of the compound should be investigated in pathological conditions related to increased sympathetic neuronal activity.

Keywords α_2 -adrenoceptor agonists blood pressure noradrenaline sedation sympathetic nervous activity

Introduction

Medetomidine (4(5)-(1-(2,3-dimethylphenyl)ethyl)imidazole; MPV 785; see Figure 1 for structure) is a novel imidazole derivative synthesized by Farmos Group Ltd (Karjalainen, 1981) as part of a research project investigating the pharmacological properties of this class of non-phenethylamine substances active at α -adrenoceptors. It is a highly lipophilic compound (Savola *et al.*, 1986) with high affinity for α_2 -adreno-

Figure 1 Structure of medetomidine.

ceptors and no or negligible binding to or effects at opiate, adenosine, dopamine, histamine or 5-HT receptors (Virtanen, 1985; Virtanen & Nyman, unpublished observations).

In various pharmacological models *in vitro*, medetomidine has behaved like a selective and potent α_2 -adrenoceptor agonist, displaying weak partial α_1 -adrenoceptor agonistic effects at high concentrations (Virtanen, 1985; Savola *et al.*, 1986). Its α_2/α_1 -binding selectivity ratio was determined to be 5060 (*vs* 970 for clonidine, Scheinin & Virtanen, 1986). It is a potent sedative in newborn chicks (Savola *et al.*, 1986), and in mice and rats (Virtanen, 1985; Scheinin *et al.*, 1986). In anaesthetised rats, it has reduced blood pressure (BP) and heart rate (HR) dose-dependently, and in the pithed rat it has elicited peripheral α_2 -adrenoceptor mediated vasoconstriction and inhibition of electrically induced tachycardia (Savola *et al.*, 1986). Biochemical experiments in rats have indicated that the compound reduces the release and metabolism of noradrenaline (NA) in the central nervous system (CNS) (Scheinin *et al.*, 1986). Idazoxan and other α_2 -adrenoceptor antagonists, but not prazosin, have antagonized these effects (Virtanen, 1985; Scheinin, 1986; Savola *et al.*, 1986).

We have recently conducted an open dose-finding and tolerability study with medetomidine in male volunteers (Scheinin *et al.*, 1987a). Single intravenous doses of 1–120 μ g were well tolerated. At doses of 40 μ g and greater, the drug appeared to suppress sympathetic neuronal activity quite potently, with marked reductions in plasma NA levels and significant decreases in BP and HR. In addition, the compound had distinct sedative properties, and it stimulated powerfully the secretion of human growth hormone, effects which are compatible with an α_2 -adrenoceptor agonistic mechanism of action (Scheinin *et al.*, 1987a).

We have now administered three different doses of medetomidine and saline placebo intravenously to eight healthy male volunteers in a double-blind experiment, with the aim of obtaining more information of the drug's effects on the level of vigilance and sympatho-adrenal function. Dissociation of sedative and cardiovascular actions has been a goal in the development of new α_2 -adrenoceptor agonists (Reid, 1981; Sweet, 1984), and in this study we sought quantitative information of the dosage of medetomidine associated with these effects.

Methods

The subjects were eight healthy male volunteers,

who participated after written informed consent (mean age, 28 years, range 24–33 years; mean weight, 82 kg, range 72–90 kg; mean height, 180 cm, range 177–186 cm). One was a smoker. The health of the subjects was ascertained by detailed medical history, physical examination, clinical chemistry tests and ECG. They had taken no medications in the 2 weeks preceding this study. Alcoholic beverages were prohibited for 36 h prior to each session, and smoking, caffeinated beverages and chocolate were not allowed from 22.00 h on the preceding night. The protocol was approved by the Ethics Committee of Turku University Hospital and the Finnish National Board of Health.

The subjects arrived at the hospital at 07.30 h fasting. Intravenous cannulae were inserted in both cubital fossae and kept open with a dilute solution of heparin. Cardiac impulse conduction and rhythm were continuously monitored (Nihon Kohden Cardioline or Kone 573). Blood pressure and heart rate were measured non-invasively with an automated oscillometric device (Nippon Colin 203Y). The experiments were performed in a quiet, dimly lit room.

Drug-induced sedation was assessed using a 10 cm long horizontal visual analogue scale (VAS) where the subjects indicated their own estimate of their level of vigilance (extremes: fully alert–almost asleep) and by determining the critical flicker fusion threshold (c.f.f.) (Smith & Misiak, 1976). Other subjective treatment-related effects were assessed by repeating a standard questionnaire at frequent intervals, and by urging the subjects to report all possibly drug-related symptoms and signs to the investigators. Basal (non-stimulated) saliva secretion was measured using three pre-weighed dental cotton rolls, placed at the orifices of the parotid ducts and sublingually for 2 min.

Blood samples were obtained for the determination of NA and adrenaline in plasma, and for analysis of anterior pituitary hormone levels (to be reported separately). Endogenous catecholamines in plasma were determined using high performance liquid chromatography with electrochemical detection (Scheinin *et al.*, 1987b, modified from Goldstein *et al.*, 1981). The reproducibility of the determination was tested using three plasma samples pooled from previous clinical studies. The resulting intra-assay coefficients of variation were < 2% for NA (concentrations 0.4–3.4 nmol l⁻¹) and approximately 10% for adrenaline (concentrations 0.04–0.21 nmol l⁻¹) (*n* = 6 for each sample).

Body weight and temperature were measured at the beginning and end of each session. Fluid intake and urine volume were also recorded.

The clinical chemistry tests were repeated after the last sessions.

The doses of medetomidine and saline placebo were administered using two replicated latin squares, with subjects and investigators unaware of the schedule. The doses were given between 08.30 and 09.00 h, after a minimum of 30 min supine rest, as 5 min intravenous infusions in a volume of 5 ml. The drug (medetomidine HCl) was dissolved in physiological saline. Measurements and sampling were performed frequently during the first 3 h (see Figures 2–8), during which time the subjects remained supine. Thereafter, a lunch was served, and visits to the lavatory were permitted. In the afternoon the subjects again rested supine until 6 h after drug administration, but were permitted to read, with less frequent measurements.

The results are presented as means $\pm$ s.d. The statistical evaluation was carried out using analysis of variance (ANOVA) for repeated measurements, with two within-factors (dose and time), computed with BMDP2V programs (BMDP Statistical Software, Inc., USA). When a significant dose effect or dose $\times$ time interaction was present, the analysis was continued by performing separate ANOVAs for each pair of successive dose levels, in order to characterize the dose-dependency of the various effects in more detail. Separate analyses were performed for the first 3 h period after drug administration and for the later time points in order to eliminate the confounding effects of the lunch break on the results, and for the -15 to $+15$ min period for BP and HR, in order to disclose possible initial injection-related effects. The P -values given in connection with ANOVAs are Greenhouse-Geisser probabilities, when pooled orthogonal components showed non-sphericity (Keselman & Keselman, 1984). Log-transformation of the data was performed when variances were unequal (saliva secretion and plasma NA). For systolic BP, the only variable with statistically significant drug effects still present at 4–6 h, the different doses were compared with placebo using the modified t -test described by Winer (1981). Subjective sedation scores (VAS) were compared using Friedman's non-parametric two-way ANOVA and the Wilcoxon signed ranks test (BMDP3S programs).

Results

Safety and tolerability

The drug was well tolerated, with no distinctly unpleasant subjective experiences. Apart from a feeling of placid tiredness after higher doses,

only dryness of the mouth was reported by all subjects (doses 25–100 μ g). This effect was rated as 'moderate' by one subject after 25 and 50 μ g and by three subjects after 100 μ g, and as 'severe' by one subject after 100 μ g, and was present 10–120 min after dosing. In addition, light-headedness was reported by one subject soon after the 50 and 100 μ g injections, and slight nasal congestion also by one subject after 100 μ g. Mood-elevating or -depressing effects were not reported.

The drug-induced hypotension and bradycardia (see below) were not related to subjective symptoms, and no symptomatic orthostatic reactions occurred 3 h after the injections when the subjects were allowed to stand up. Cardiac monitoring did not reveal any disturbances in impulse generation or conduction. No increases in body temperature were seen. Urine volumes were relatively constant over the different sessions, with no dose-related changes. The clinical chemistry tests performed after this series of injections did not give abnormal values in any of the volunteers.

Blood pressure and heart rate

Systolic and diastolic BP and HR were dose-dependently reduced after the injections (Figures 2, 3 and 4) ($F = 36.91$, $P = 0.000$; $F = 45.24$, $P = 0.000$; and $F = 7.36$, $P = 0.002$, respectively; differences between dose levels also statistically significant, except for HR between placebo and 25 μ g, and between 25 and 50 μ g). Maximal average BP reductions amounted to 18/11 mm Hg after 100 μ g (from $113 \pm 7/67 \pm 6$ to $95 \pm 9/56 \pm 7$ mm Hg), and occurred 30–120 min after dosing (maximal individual reductions 10/10–28/19 mm Hg). An initial hypertensive response was not seen, but the BP fall started only after the 50 and 100 μ g injections had been completed, not during the injections (see inserts in Figures 2 and 3). At 4 h ($P < 0.01$) and at 5 h ($P < 0.05$) systolic BP was still reduced after the 50 and 100 μ g doses, but by 6 h there were no differences in BP between the various dose levels (modified t -test). HR was initially sharply and statistically significantly reduced during the 50 and 100 μ g injections ($F = 2.96$, $P = 0.044$ for dose $\times$ time interaction, $P < 0.01$ for differences from placebo for 50 and 100 μ g), returned to baseline at 7.5–10 min, and was maximally reduced by 7–10 beats min^{-1} 30–180 min after 100 μ g (from 58 ± 7 to 48 ± 4 beats min^{-1} at 120 min) (Figure 4).

Sedative effects

Dose-dependent sedative effects were observed using both objective (c.f.f.) and subjective

Figure 2 Average systolic blood pressure of eight healthy male volunteers after single intravenous doses of medetomidine. $\circ$ saline placebo; $\bullet$ 25 μg ; $\triangle$ 50 μg ; $\blacktriangle$ 100 μg . Standard deviations have been omitted for clarity (see text for typical examples). Insert: -15 to +15 min in greater detail.

Figure 3 Average diastolic blood pressure after single intravenous doses of medetomidine. $\circ$ saline placebo; $\bullet$ 25 μg ; $\triangle$ 50 μg ; $\blacktriangle$ 100 μg . Insert as in Figure 2.

(VAS) assessments (Figures 5 and 6) ($F = 23.12$, $P = 0.001$ for c.f.f.; $P = 0.10$ for difference between placebo and 25 μg , $P = 0.03$ between 25 and 50 μg , and $P = 0.05$ between 50 and 100 μg). The flicker fusion threshold was reduced from an initial value of 27.6 ± 1.5 Hz to 22.0 ± 2.2 Hz at 30 min after the 100 μg dose. Drug-related subjective sleepiness appeared quite rapidly (NS at 5 min, $P < 0.001$ at 10 min, Friedman's ANOVA), was maximal at 15–45 min, and was also swift to disappear ($P < 0.05$ at 3 h, NS at 4 h). Five of the subjects actually fell asleep several times after the highest dose, but could easily be awakened for the measurements. VAS scores after placebo and the 25 μg dose were

significantly different from 10 min ($P = 0.02$) until 60 min after drug administration ($P = 0.03$, Wilcoxon's test).

Saliva secretion

Basal (non-stimulated) salivation was dose-dependently reduced after the injections ($F = 69.93$, $P = 0.0001$; all differences between doses also significant at $P < 0.02$). The highest dose produced up to 84% average reductions in saliva secretion at 15–60 min (from 0.87 ± 0.30 g 2 min^{-1} at -15 min to 0.14 ± 0.04 g 2 min^{-1} at 30 min). At 3 h, there were only slight differences between the dose levels (Figure 7).

Figure 4 Average heart rate after single intravenous doses of medetomidine. $\circ$ saline placebo; $\bullet$ 25 μg ; $\triangle$ 50 μg ; $\blacktriangle$ 100 μg . Insert as in Figure 2.

Figure 5 Average values for the critical flicker fusion threshold (c.f.f.) after medetomidine. $\circ$ saline placebo; $\bullet$ 25 μg ; $\triangle$ 50 μg ; $\blacktriangle$ 100 μg .

Catecholamines in plasma

The concentration of NA in plasma was potently and dose-dependently reduced after medetomidine (Figure 8) ($F = 26.15$, $P = 0.001$; all differences between doses also significant at $P < 0.05$). The highest dose reduced plasma NA from an average basal value of $0.97 \pm 0.58 \text{ nmol l}^{-1}$ to $0.28 \pm 0.15 \text{ nmol l}^{-1}$ at 15 min. This 70% average decrease was maintained until 60 min after dosing. In one subject, plasma NA actually fell below the limit of reliable detection of the assay, 0.02 nmol l^{-1} . The 25 μg dose reduced NA in plasma by 37%, on the average (from $1.02 \pm$

0.46 to $0.63 \pm 0.26 \text{ nmol l}^{-1}$ at 15 min and $0.67 \pm 0.35 \text{ nmol l}^{-1}$ at 30 min). Adrenaline in plasma was apparently uninfluenced by the drug ($F = 2.27$, $P = 0.11$ for dose effect, $F = 1.31$, $P = 0.29$ for dose $\times$ time interaction), showing a slightly decreasing tendency after all treatments ($F = 3.16$, $P = 0.04$) (e.g., from 0.06 ± 0.03 to $0.04 \pm 0.02 \text{ nmol l}^{-1}$ after 100 μg ; data not shown).

Discussion

Medetomidine has emerged from *in vitro* and *in vivo* animal experiments as a potent, selective

Figure 6 Median values for subjectively estimated sedation (as mm on a 100 mm long visual analogue scale, VAS) after medetomidine. 0 = fully alert; 100 = almost asleep. ○ saline placebo; ● 25 µg; △ 50 µg; ▲ 100 µg.

Figure 7 After saliva secretion (as g 2 min⁻¹) after medetomidine. ○ saline placebo; ● 25 µg; △ 50 µg; ▲ 100 µg.

and specific α_2 -adrenoceptor agonist, with a wide margin of safety in toxicological studies. Its pharmacological effects in animals include hypotension, bradycardia, sedation and analgesia. Its effects on behaviour are associated with reductions in the release and turnover of NA in the CNS (Virtanen, 1985; Scheinin *et al.*, 1986; Savola *et al.*, 1986).

In our previous open pilot study (Scheinin *et al.*, 1987a), intravenously administered single doses of medetomidine were related to decreases in systolic and diastolic BP, HR, saliva secretion, and NA levels in plasma. Drug-related sedation was also observed. The present study was conducted to verify these observations under double-blind conditions and to obtain quantitative information of the dose-dependency of the different effects.

Figure 8 Average noradrenaline (NA) concentrations in plasma after single intravenous doses of medetomidine. ○ saline placebo; ● 25 µg; △ 50 µg; ▲ 100 µg.

The powerful reducing effect of medetomidine on the concentration of NA in plasma (70% after 100 µg) points to inhibition of sympathetic neuronal activity as an important mechanism for the drug's action. Similar reductions in plasma NA have been reported in healthy volunteers after 300 µg oral or intravenous doses of clonidine (Wing *et al.*, 1977; Hossman *et al.*, 1980). Plasma NA levels are determined by the rate of influx of

NA to plasma and the plasma clearance of NA, and drugs may affect plasma NA levels by modifying either of these determinants. Radio-tracer methods have previously been used to demonstrate that the reduction in plasma NA levels after clonidine is solely due to reduced release and spillover into plasma of NA, and not increased clearance of NA from plasma (Esler *et al.*, 1982).

Hypotension induced by vasodilators, such as nitroprusside, is a powerful stimulus for both NA and adrenaline release in man: an average 15% reduction in diastolic blood pressure has increased plasma NA by 120% (Grossman *et al.*, 1982), and an average 20 mm Hg reduction in mean arterial pressure, in connection with hypotensive anaesthesia and surgery, was associated with approximately ten-fold elevations in the plasma levels of both catecholamines (Knight *et al.*, 1983). It thus appears that medetomidine not only reduced NA release from sympathetic nerve endings, but possibly also inhibited hypotension-induced adrenomedullary secretion.

The hypotensive effect of clonidine is mediated by activation of α_2 -adrenoceptors located in the central nervous system, and is directly related to decreased sympathetic activity (Reid *et al.*, 1977a,b, Reid, 1981; Kobinger, 1983; van Zwieten *et al.*, 1984). On the other hand, the bradycardic action of clonidine is demonstrable also in tetraplegic patients with cervical spinal cord transections above the level of sympathetic outflow (Reid *et al.*, 1977b), which does not give support for the importance of reduced sympathetic efferent outflow to the heart or activation of presynaptic cardiac α_2 -adrenoceptors in mediating this effect (van Zwieten *et al.*, 1984). Instead, a centrally mediated increase in efferent vagal activity has been proposed as the mechanism inducing bradycardia after clonidine (Dollery *et al.*, 1976; Reid *et al.*, 1977a,b; van Zwieten *et al.*, 1984).

Medetomidine decreased BP in our subjects quite rapidly, with fully developed effects 5 min after the completion of the 25 μ g injection and 25 min after the 100 μ g dose. The maximal average hypotensive effect of 100 μ g medetomidine was slightly less than that reported previously after 300 μ g clonidine intravenously in healthy subjects, *viz.* 18/11 mm Hg vs 26/16 mm Hg (Davies *et al.*, 1977), 20/13 mm Hg (Reid *et al.*, 1977b), or 28/18 mm Hg (Wing *et al.*, 1977), but the onset of the effect was somewhat more rapid and its duration was clearly shorter after medetomidine than after clonidine. The time course of the BP reduction in our subjects (Figures 2 and 3) paralleled very closely the temporal patterns of drug-induced sedation (Figures 5 and 6) and the

reduction of NA in plasma (Figure 8), which would appear to give support for a centrally mediated decrease in sympathetic neuronal activity as the mechanism for the BP reduction.

Heart rate was transiently reduced during the 50 and 100 μ g injections, returned to baseline, and was then gradually decreased in a dose-related manner (Figure 4). On the whole, the bradycardic effect of medetomidine was rather modest, as has also been reported for single intravenous doses of clonidine in normal subjects (Davies *et al.*, 1977; Reid *et al.*, 1977b; Wing *et al.*, 1977). Sedation was not assessed during the injections, but at the end of the 5 min injection it was still developing and far from maximal, and was thus dissociated from the initial bradycardia. This would argue against direct drug effects in the CNS as a mechanism for increased vagal activity in the initial phase, and suggests the involvement of a peripheral component, most likely aortic baroreceptor-mediated reflex vagal efferent activation (Reid *et al.*, 1977a,b; Grossman *et al.*, 1982; van Zwieten *et al.*, 1984). Initial BP increases during the injections were not seen in our subjects (see inserts in Figures 2 and 3), but large intravenous doses of medetomidine have caused short-lived initial BP increases in experimental animals via activation of α_2 -adrenoceptors on vascular smooth muscle (Savola *et al.*, 1986). An initial vasoconstrictor effect and slight BP rise in humans might only be demonstrable with direct arterial BP measurements.

Impaired salivation is a well-known side-effect of clonidine, and 300 μ g single doses have reduced salivary flow in normal subjects and tetraplegic patients by up to 90%, with very prominent effects still present at 8 h after administration (Dollery *et al.*, 1976; Davies *et al.*, 1977; Reid *et al.*, 1977b). The mechanism was initially suggested to involve a central drug action on the parasympathetic innervation of the salivary glands (Reid *et al.*, 1977b), but there is also evidence in favour of a peripheral attenuating effect on acetylcholine release, possibly mediated by inhibitory presynaptic α_2 -adrenoceptors on parasympathetic neurons (Green *et al.*, 1979).

α_2 -adrenoceptor agonists cause sedation by reducing the firing rate of noradrenergic coeruleo-cortical neurons which maintain wakefulness (Cedarbaum & Aghajanian, 1977). Sleepiness is a troublesome side effect in the treatment of hypertension with clonidine (Reid, 1981; Sweet, 1984; van Zwieten *et al.*, 1984). In spite of considerable effort, drug developers have so far been unable to dissociate impairment of vigilance from the cardiovascular effects of α_2 -adrenoceptor agonist drugs (Reid, 1981; Sweet, 1984).

On the other hand, the combined sedative, anxiolytic and sympatholytic properties of clonidine have been used successfully in the therapy of various neuropsychiatric disorders associated with increased sympathetic neuronal activity, such as opiate withdrawal (Gold *et al.*, 1978), cigarette craving and withdrawal symptoms in smokers (Glassman *et al.*, 1984), and generalized and panic anxiety (Redmond, 1982). Also in the case of medetomidine, at least in normal subjects without pathological anxiety, the sedative and hypotensive drug actions seem to manifest in the same dose range, with a single 25 µg intravenous dose causing statistically significant sedation and reduction of BP. This does not, however, preclude even lower doses from having more selective beneficial sedative or anxiolytic effects in patients with symptoms related to noradrenergic overactivity.

All observed pharmacodynamic effects of medetomidine were compatible with an α_2 -adrenoceptor agonistic mechanism of action. Essentially similar effects, but with a different time course, have been observed after intravenous administration of clonidine to healthy subjects. Whereas most of the effects of medetomidine had subsided by 3 h after drug administration, the hypotension, dry mouth and seda-

tion produced by clonidine are still prominent at 8 h (Davies *et al.*, 1977; Reid *et al.*, 1977b; Wing *et al.*, 1977).

Further studies, with more sophisticated assessments of e.g. haemodynamic and CNS effects, and also using established pharmacological agents for purposes of comparison (e.g., clonidine and diazepam), are required to establish the exact pharmacodynamic profile of medetomidine in healthy humans and to disclose any possible differences between the effects of this new derivative and clonidine. The compound may have therapeutic potential in pathological neuropsychiatric and cardiovascular conditions related to increased sympathetic neuronal activity. It may also be a useful aid in the diagnosis of pheochromocytoma, where a short-acting drug would appear to have advantages over clonidine. In addition, after full clinical pharmacological validation, medetomidine may prove to be a valuable tool for the pharmacological and physiological investigation of α_2 -adrenoceptors in humans.

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References

- Cedarbaum, J. M. & Aghajanian, G. K. (1977). Catecholamine receptors in locus coeruleus neurons: Pharmacological characterization. *Eur. J. Pharmac.*, **44**, 375–385.
- Davies, D. S., Wing, L. M. H., Reid, J. L., Neill, E., Tippet, P. & Dollery, C. T. (1977). Pharmacokinetics and concentration-effect relationships of intravenous and oral clonidine. *Clin. Pharmac. Ther.*, **21**, 593–601.
- Dollery, C. T., Davies, D. S., Draffan, G. H., Dargie, H. J., Dean, C. R., Reid, J. L., Clare, R. A. & Murray, S. (1976). Clinical pharmacology and pharmacokinetics of clonidine. *Clin. Pharmac. Ther.*, **19**, 11–17.
- Esler, M., Leonard, P., O'Dea, K., Jackman, G., Jennings, G. & Korner, P. (1982). Biochemical quantification of sympathetic nervous activity in humans using radiotracer methodology: fallibility of plasma noradrenaline measurements. *J. cardiovascular. Pharmac.*, **4**, S152–S157.
- Glassman, A. H., Jackson, W. K., Walsh, B. T., Roose, S. P. & Rosenfeld, B. (1984). Cigarette craving, smoking withdrawal, and clonidine. *Science*, **226**, 864–866.
- Gold, M. S., Redmond, D. E. Jr. & Kleber, H. D. (1978). Clonidine blocks acute opiate-withdrawal symptoms. *Lancet*, **ii**, 599–602.
- Goldstein, D. S., Feuerstein, G., Izzo, J. L., Kopin, I. J. & Keiser, H. R. (1981). Validity and reliability of liquid chromatography with electrochemical detection for measuring plasma levels of norepinephrine and epinephrine in man. *Life Sci.*, **28**, 467–476.
- Green, G. J., Wilson, H. & Yates, M. S. (1979). The effect of clonidine on centrally and peripherally evoked submaxillary salivation. *Eur. J. Pharmac.*, **53**, 297–300.
- Grossman, S. H., Davis, D., Gunnells, J. C. & Shand, D. G. (1982). Plasma norepinephrine in the evaluation of baroreceptor function in humans. *Hypertension*, **4**, 566–571.
- Hossmann, V., Maling, T. J. B., Hamilton, C. A., Reid, J. L. & Dollery, C. T. (1980). Sedative and cardiovascular effects of clonidine and nitrazepam. *Clin. Pharmac. Ther.*, **28**, 167–176.
- Karjalainen, A. (1981). On the design and synthesis of antihypertensive 4(5)-substituted imidazole derivatives. *Acta Univ. Oul.* A125. Chem 15, Oulu.
- Keselman, H. J. & Keselman, J. C. (1984). The analysis of repeated measures design in medical research. *Stat. Med.*, **3**, 185–195.
- Knight, P. R., Lane, G. A., Hensinger, R. N., Bolles, R. S. & Bjoraker, D. G. (1983). Catecholamine and renin-angiotensin response during hypotensive anesthesia induced by sodium nitroprusside or trimetaphan camsylate. *Anesthesiology*, **59**, 248–253.

- Kobinger, W. (1983). Central blood pressure regulation. Involvement of presynaptic or postsynaptic α_1 - or α_2 -adrenoceptors? *Chest*, **83**, supplement, 296–299.
- Redmond, D. E. Jr. (1982). Does clonidine alter anxiety in humans? *Trends pharmac. Sci.*, **3**, 477–480.
- Reid, J. L. (1981). The clinical pharmacology of clonidine and related central antihypertensive drugs. *Br. J. clin. Pharmac.*, **12**, 295–302.
- Reid, J. L., Tangri, K. K. & Wing, L. M. H. (1977a). The central hypotensive action of clonidine and propranolol in animals and man. *Prog. Brain Res.*, **4**, 369–383.
- Reid, J. L., Wing, L. M. H., Mathias, C. J., Frankel, H. L. & Neill, E. (1977b). The central hypotensive effect of clonidine. Studies in tetraplegic subjects. *Clin. Pharmac. Ther.*, **21**, 375–381.
- Savola, J.-M., Ruskoaho, H., Puurunen, J., Salonen, J. S. & Kärki, N. T. (1986). Evidence for medetomidine as a selective and potent agonist of α_2 -adrenoceptors. *J. auton. Pharmac.*, **5**, 275–284.
- Scheinin, H. (1986). Enhanced noradrenergic neuronal activity increases homovanillic acid levels in cerebrospinal fluid. *J. Neurochem.*, **47**, 665–667.
- Scheinin, H. & Virtanen, R. (1986). Medetomidine, a novel α_2 -agonist. Abstract, 25th Annual Meeting of the American College of Neuro-Psychopharmacology, Dec. 8–12, Washington, D.C., p. 238.
- Scheinin, H., Virtanen, R. & Scheinin, M. (1986). α_2 -adrenoceptor agonists decrease free 3-methoxy-4-hydroxyphenylglycol in rat cerebrospinal fluid. *Eur. J. Pharmac.*, **123**, 115–121.
- Scheinin, M., Kallio, A., Koulou, M., Arstila, M., Viikari, J. & Scheinin, H. (1987a). Dose-finding and tolerability study of medetomidine in four healthy volunteers—an open phase I investigation. *Curr. ther. Res.*, **41**, 637–646.
- Scheinin, M., Koulou, M., Laurikainen, E. & Allonen, H. (1987b). Hypokalaemia and other non-bronchial effects of inhaled fenoterol and salbutamol: A placebo-controlled dose-response study in healthy volunteers. *Br. J. clin. Pharmac.* (in press).
- Smith, J. M. & Misiak, H. (1976). Critical flicker frequency (CFF) and psychotropic drugs in normal subjects—a review. *Psychopharmacology*, **47**, 175–182.
- Sweet, C. S. (1984). New centrally acting antihypertensive drugs related to methyldopa and clonidine. *Hypertension*, **6** (suppl. II), 51–56.
- van Zwieten, P. A., Thoolen, M. J. M. C. & Timmermans, P. B. M. W. M. (1984). The hypotensive activity and side effects of methyldopa, clonidine, and guanfacine. *Hypertension*, **6** (suppl. II), 28–33.
- Virtanen, R. (1985). Detomidine and MPV-785, two sedative/analgesic imidazole derivatives with different species selectivity. Abstract, 3rd Congress of the European Association for Veterinary Pharmacology and Toxicology, Aug. 25–29, Ghent, Belgium, p. 39.
- Winer, B. J. (1971). *Statistical principles in experimental design*, 2nd edn New York: McGraw-Hill.
- Wing, L. M. H., Reid, J. L., Hamilton, C. A., Sever, P., Davies, D. S. & Dollery, C. T. (1977). Effects of clonidine on biochemical indices of sympathetic function and plasma renin activity in normotensive man. *Clin. Sci. mol. Med.*, **53**, 45–53.

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