serum in the blood-samples are expressed as counts per unit time. These expressions of quantity are then used to find the occupancy in the same way as if they were μg.

Optimal Daily Dosage

Total Dosage

The total daily dosage required to maintain the desired optimal average serum-level is found using occupancy in the formula:

$$\text{Total daily dosage} = \frac{\text{Desired serum-level}}{\text{Occupancy (hr.)}} \times 24$$

In the above three examples the total daily dosage to maintain average serum-levels of 5 μg. per ml. would be:

(*A*) $\frac{5}{0{\cdot}29 \times 10^{-3}} \times 24$ μg. = 410 mg. gentamicin

(*B*) $\frac{5}{43{\cdot}8 \times 10^{-6}} \times 24$ μg. = 2·75 mg. tetracycline

(*C*) $\frac{5}{0{\cdot}95 \times 10^{-3}} \times 24$ μg. = 125 mg. kanamycin

The equation is an expression of the occupancy principle in a form suitable for the pharmacological problem. The principle has a general validity, but the use of the method described above to measure occupancy requires that a dose of a drug should be absorbed and disappear in the same manner whether it is given as a first dose or after the blood-level has reached an equilibrium value. Exceptions to this condition are rare.[7]

Interval between Doses

More attention should be paid to the interval between administrations of the drug. If the drug to be used is an antibiotic, the minimum desired level will be the minimum inhibitory concentration (M.I.C.) of the drug for the organism, and the maximum level should be below the known toxic serum-level of the drug. If this minimum is half the maximum, then the time interval between doses should not be greater than the time taken for the serum concentration after a test dose to fall to half of its maximum. The desired average level will lie approximately midway between the desired minimum and maximum.

For example, if the M.I.C. of kanamycin for a particular organism is 4 μg. per ml. and the toxic level is 16 μg. per ml. the intention might be to keep between 12 and 6 μg. per ml. Using the example shown in fig. 4 the maximum concentration after the test dose is 26 μg. per ml. and the concentration has fallen to 13 μg. per ml. after 12 hours. Therefore a 12-hour interval between administrations is appropriate in this case. The desired average level would then be 9 μg. per ml. requiring a total daily dosage of 225 mg.

When administration is by constant infusion, such as with cytotoxic drugs, the serum-level attained should be constant and will equal the desired level.

Conclusion

The problem of toxic drug accumulation in pharmacotherapeutics is a serious one, and the need for a theory of drug accumulation which can be used by the practising physician has been emphasised before.[8] The approach described here is formally correct irrespective of the method of administration, and is presented in a formulation designed for simple everyday use.

The concept of occupancy and the occupancy principle have been applied to studies of the kinetics of a wide variety of metabolic problems. These include iodine,[9] thyroid hormones,[10] calcium absorption and accretion, iron, bromine, trace elements, and radiation dose from ingested isotopes.[11] This application to pharmacology forms a junction between one of the diverse developments stemming from the occupancy principle and the successful application of pharmacokinetics to the analysis and solution of problems in pharmacotherapeutics.

Requests for reprints should be addressed to J. S. O.

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ARTERIAL BLOOD GASES AFTER ATROPINE SULPHATE IN HEALTHY VOLUNTEERS

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Summary The effects of atropine 0·6 mg. intravenously administered to ten healthy volunteers in recumbent position, on arterial pH, P_aCO_2, and P_aO_2 were determined; there were no significant alterations of blood gas values after atropine administration. There seems to be no contraindication to the use of atropine sulphate for premedication in terms of its effect upon arterial blood-gases, in patients with normal cardiorespiratory function.

Introduction

IN 1964, Tomlin et al.[1] reported a finding that would potentially limit the use of atropine. They presented data which showed a fall in P_aO_2 after intramuscular atropine.

We have evaluated the effects of intravenous atropine sulphate on arterial blood gases in healthy volunteers.

Method

The nine volunteers were healthy adult students between the ages of 21 and 29 (mean 25). They ranged in height from 64 to 73·5 in. with a mean of 69 in., and weighed from 115 to 210 lb. (mean 154 lb.). Three were female. All consented to the administration of atropine and to arterial puncture. The volunteers were recumbent during the tests.

Blood-samples were obtained via an indwelling Riley needle inserted into the left brachial artery. P_aO_2 was determined polarographically, using a Radiometer-Clark electrode. pH was determined using a Radiometer glass

MEAN (±S.D.) P_{aO_2} P_{aCO_2}, AND pH in HEALTHY VOLUNTEERS GIVEN 0·6 mg. ATROPINE

	Control values		Post-atropine values at (min.):					
	1	2	5	15	30	45	60*	Post sigh
P_{aO_2} (mm. Hg)	93·88 (±4·09)	93·22 (±5·16)	93·33 (±4·76)	91·66 (±5·37)	93·11 (±4·53)	92·88 (±4·75)	92·88 (±5·68)	93·88 (±4·60)
P_{aCO_2} (mm. Hg)..	35·5 (±3·54)	36·2 (±3·26)	34·2 (±2·66)	33·3 (±5·87)	35·3 (±3·68)	36·4 (±7·74)	35·1 (±4·17)	32·2 (±5·99)
pH	7·40 (±0·018)	7·40 (±0·021)	7·40 (±0·016)	7·40 (±0·02)	7·39 (±0·012)	7·38 (±0·033)	7·39 (±0·018)	7·41 (±0·035)

* Results for eight volunteers only; one sample was contaminated.

electrode with carbon-dioxide tensions being interpolated by the Siggaard Anderson method.

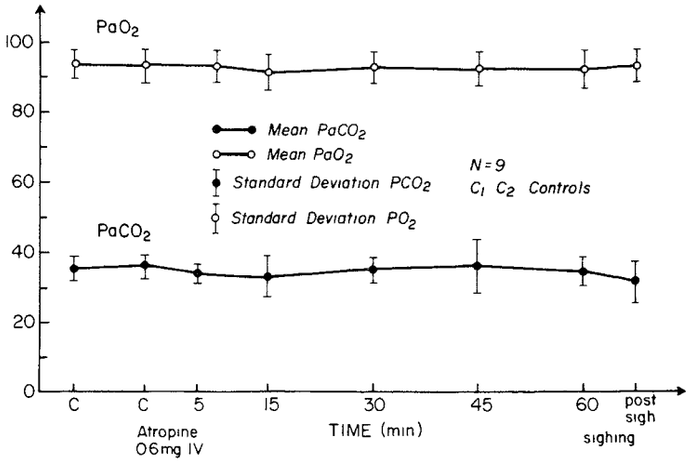
Lead II of the electrocardiograph was monitored during the procedure in eight volunteers.

After insertion of the intra-arterial needle and the start of an intravenous infusion of 5% glucose and 0·2% sodium chloride a period of rest was allowed. Two arterial samples were then drawn at 10-minute intervals.

Atropine sulphate 0·6 mg. was given intravenously in a volume of 20 ml. and over a period of 2 minutes, and blood-samples were drawn at intervals of 5, 15, 30, 45, and 60 minutes. Volunteers were then asked to take a maximum inspiration three times during a 1-minute period. 5 minutes later, a final arterial sample was drawn.

Results

P_{aO_2} levels did not change significantly at any time during the monitoring period, and P_{aCO_2} levels remained within physiological limits throughout the test (see figure and table). Variations in pH were not significant (see table).



There were no arrhythmias associated with atropine administration in any volunteer. Pulse-rate ranged from a mean of 85 just before administration of the drug to a mean of 103 afterwards; these changes were not felt to be of clinical significance.

Discussion

In attempting to reconcile our results with those of Tomlin et al.[1] some comments on their study should be made:

(1) We used healthy volunteers while Tomlin et al. investigated patients preoperatively.

(2) Tomlin et al. took no control samples before administration of atropine, so they did not, in fact, demonstrate a fall in P_{aO_2} in any patient after the drug. All they did demonstrate was a difference in P_{aO_2} between two groups of patients immediately before induction of general anæsthesia; one group having received atropine.

(3) Three of their control patients had P_{aO_2} levels above 102 mm. Hg, one being as high as 111·9 mm. Hg. These are somewhat difficult to reconcile in a patient breathing room air.

Our results are corroborated by Daly et al.[2] who found no fall in P_{aO_2} in healthy volunteers after intramuscular administration of atropine sulphate.

Atropine sulphate given intravenously does not seem to produce changes in blood gases in healthy volunteers. We conclude that no contraindication to atropine as an adjunct to premedication exists in so far as its effect on arterial oxygenation is concerned. Additional studies in patients with cardiopulmonary problems are needed.

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Requests for reprints should be addressed to J. S. F.

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Preliminary Communications

RECOVERY OF RESISTANCE (R) FACTORS FROM A DRUG-FREE COMMUNITY

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Summary A study of an antibiotic virgin population in the Solomon Islands showed that R factors can be recovered at low frequency under natural conditions without the selective force of antimicrobial drugs. These R factors were recovered from soil and stool specimens, mediated resistance to streptomycin and tetracycline, and, like certain R factors recovered in the United States, inactivated streptomycin by phosphorylation.

INTRODUCTION

DESPITE the worldwide distribution of resistance (R) factors, the origin of these episomes remains