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EVALUATION OF ANTIMUSCARINIC ACTIVITY IN HUMAN VOLUNTEERS: A TEACHING AID IN CLINICAL PHARMACOLOGY

S. K. TRIPATHI, C. R. GRIYAPPANAVAR, A. LAL, K. BISWAS, N. R. BISWAS, A. SANKARANARAYANAN AND P. L. SHARMA*

Department of Pharmacology, Postgraduate Institute of Medical Education and Research, Chandigarh - 160 012

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Abstract: The antimuscarinic activity of oxyphenonium bromide, diphenhydramine hydrochloride and astemizole were evaluated in six volunteers. The parameters used were salivary secretion, heart rate and pupillary size. The results indicated that the changes in heart rate and pupillary size and measurements were not convenient parameters for class room demonstration. However, salivary secretion and dryness of mouth were found to be reliable parameters for measurement. It was concluded that simple procedures like evaluation of antimuscarinic activity could be introduced as teaching aids in clinical pharmacology for undergraduate students.

Key words: teaching aid clinical pharmacology undergraduate

INTRODUCTION

To a medical student, the study of pharmacology should be clinically oriented (1). The teaching-learning of pharmacology in undergraduate medical training programmes in India, at present is neither rationally planned, nor optimally need-oriented, and has little relevance to what is practised at the bed side (2).

In the course curriculum of any technical scientific discipline, the importance of practical excercises - 'doing it self' or "self learning" is universally accepted. In pharmacology also, the undergraduate students are exposed to practical exercises. In India, however, practical exercises, which ceased to have any clinical relevance long ago, or have become obsolete, are still included in the curriculum (2). Understandbly, the student develops a negative and/or mechanical attitude towards such practical sessions. To make the subject more interesting and relevant to their future needs, simple and non-invasive volunteer experiments should be introduced in the course curriculum where more basic pharma-codynamic and pharmacokinetic principles can be learnt/demonstrated.

The present study is an attempt to evolve a suitable model for demonstrating drug effects in human volunteers which could be recommended for use as a teaching aid in clinical pharmacology. The aim of this study was to develop and recommend a non-invasive, simple, yet reliable method for assessment of antimuscarinic potential of drugs as a suitable model for teaching aid in clinical pharmacology to undergraduate medical students.

METHODS

An open, controlled study was designed to evaluate the relative suitability of different clinical methods/ parameters available for assessment of antimuscarinic effect of drugs. The study was approved by the Institutional Ethical Review Committee and informed consent was obtained from all persons enrolled in the study. Three agents with graded antimuscarinic activity e.g. oxyphenonium bromide (OXP) (3) diphenhydramine hydrochloride (DPH) (4) and astemizole (AST) (5) were chosen for this purpose. Three different parameters, i.e. decrease in salivary secretion, increase in heart rate and pupillary dilatation

*Corresponding Author

were studied as indices of antimuscarinic potential following single, oral doses of OXP (5 mg tab. - Oxyphenonium, Antrenyl) DPH (20 mg cap. - Diphenhydramine, Bendryl) and AST (10 mg- Astemizole, Stemiz), administered in that order to 6 non-smoking healthy male students (25-35 years) at 8 a.m. on three different days separated by five days. The volunteers fasted overnight and received the same standard breakfast at 6:30 a.m. on each day of experiment. The three indices for antimuscarinic activity were measured both objectively - Salivary volume (ml) (6). Heart rate (per min) and pupil diameter (mm), and subjectively by administering a visual analogue scale (VAS, 0-100 mm horizontal line: for dryness of mouth, palpitation and blurring of vision) at baseline levels and at different post-drug hours according to the known time course of effects of each drugs, at 0, ½, 1, 1½, 3 and 3½ hr for OXP at 0, 1, 2, 3, 4 and 5 hr for DPH and 0, 1, 3, 5, 8, 12 and 24 hr for AST.

A standard lunch was served at 1.30 p.m., evening tea at 5 p.m. and dinner at 9 p.m. For measurement of salivary volume, a preweighed (1 gm) piece of rock salt was kept in the mouth by the volunteers for 2 min to stimulate salivation at each time of saliva collection. Saliva was collected in a 10 ml measuring cylinder.

Heart rate (supine) was measured by palpation of radial pulse over a min period. The volunteers took rest for at least 10 min before each heart rate measurement. Pupil size was measured in both eyes by using a milimeter scale, with the volunteer sitting on chair fixed his eyes on a black closed circle of 2 cm diameter drawn on the white wall at a distance of 6 meters, at the same level as his eyes. The laboratory was artificially lighted uniformly throughout the experiment. The significance of difference between the mean values was determined using Students 't' test. Co-relation coefficient (r) between average DSV and average IDM and the maximum DSV and maximum IDM of each drug was determined by the method of linear regression calculations.

RESULTS

All the three drugs decreased the mean and the maximal salivary volume. The decrease produced by AST but not DPH was significant as compared to OXP ($P<0.01$). The values for average increase or maximal increase in dryness of mouth for the three drugs, however, were not much different. The objective and subjective evaluation data in all cases were well correlated. Besides, the time to reach the maximal effect and the dynamic half life (for average decrease

TABLE I: Antimuscarinic potential of oxyphenonium, diphenhydramine and astemizole as quantitated by salivary volume measurement and VAS-assessment of dryness of mouth.

Drugs		*Avg. DSV (ml)*	*Avg. IDM (mm)*	*Max. DSV (ml)*	*Max IDM (mm)*	*Time to max. DSV (hr)*	*Time to max. IDM (hr)*	*$t^1/_2$ for Avg. DSV (hr)*
OXP	Mean	2.17	11.69	3.04	19.33	2.58	2.80	1.36
	SEM	0.20	2.08	0.29	7.23	0.54	0.12	
	r	0.99		0.69				
DPH	Mean	1.52	10.03	2.21	20.67	4.33	3.00	2.03
	SEM	0.30	2.59	0.57	7.79	0.23	0.55	
	r	0.74		0.45				
AST	Mean	1.28*	9..81	1.87	18.83	13.00	7.60	33.50
	SEM	0.13	1.83	0.35	6.78	3.48	0.40	
		0.46		0.41				

*P< 0.01as compared to OXP

Avg. =Average, Max = maximal

IDM =Increase in dryness of mouth

DSV =Decrease in salivary volume

All values are Mean ± SEM (n=6)

'r' = correlation co-efficient between avg. DSV and IDM and between max. DSVand IDM of each drug.

in salivary volume) were consistent with the known kinetic behaviour of the three drugs (Table I).

Changes in heart rate and pupil size assessed both objectively and subjectively were inconsistant and equivocal.

DISCUSSION

The changes in salivary volume were found to be a reliable indicator of antimuscarinic potential of drugs. It is simple, non-invasive and requires minimum materials. The subjective assessment of dryness of mouth using VAS also reliably reflected antimuscarinic potential. Method is relevant and easy to perform. The VAS data correlated well with objective measurement of salivary volumes in our study.

On the contrary, both objective and subjective assessment of changes in heart rate and pupil size yielded inconsistant and equivocal data. However, this is not a surprising finding, since these parameters are nonspecific and are likely to be influenced by a variety of stimuli. Measurements of such parameters warrant special control measures which may not be convenient for routine classroom demonstration purposes. Thus, they are not very reliable indicators of antimuscarinic potential of drugs as a model for teaching aid. Possible differences in peripheral action (as manifested by salivary volume parameter) and the central action (as manifested by the ability to score the dryness of mouth using the VAS), may be responsible for the apparent difference in the 'r' value for each drug between maximum DSV and maximum IDM.

It is recommended that evaluation of antimuscarinic potential of drugs by objective (Salivary volume measurement) and subjective (dryness of mouth assessment by VAS) methods in healthy volunteers can be introduced as a teaching aid in clinical pharmacology to undergraduate medical students. This gives an opportunity for students to participitate in the study as volunteers and gives enough motivation in learning. Identification and development of simple experiments demonstrating various pharmacological effects in human volunteers, would be of value in teaching the clinical pharmacology to undergraduate students.

REFERENCES

1. Nirenberg DW. Clinical Pharmacology instruction for all medical students. *Clin Pharmacol Ther* 1986; 40: 483-487.
2. Pandhi P, Tripathi SK, Datta H, Sharma PL. Teaching-learning of Pharmacology in undergraduate medical colleges in India. *Proceedings of International Workshop on "Teaching of Clinical Pharmacology" in New Delhi* 1991; page 72.
3. Wainer N. Atropine, Scopolamine and related antimuscarine drugs. In: Gilman AG, Goodman LS, Rall TW, Murad F. The Pharmacological basis of therapeutics. The Macmillian Publishing Company, New York, 1985; 130-144.
4. Garrison UC. Histamine, Bradykinin, 5-Hydroxytrptamine and their antogonists. In: Gilman AG, Rall TW, Neis AS, Taylor P eds. The pharmacological basis of therapeutics. Macmillan Publishing Company, New York 1991; 575-599.
5. Krstenamsky PM, Cluxton RJ, Jr. Astemizole, a long acting non sedating antihistamine. *Drug Intell Clin Pharm* 1987; 21: 947-953.
6. Kingsley PJ, Turner P. Class experiment in clinical pharmacology with benzilonium bromide, an anticholinergic drug. *Eur J Clin Pharmacol* 1974; 7: 141-143.