Table 1

Acute toxicity study of *Vitex negundo* extract in albino rats

Each group (n=6)	Drug	Dose (g/kg, p.o.)	Percent mortality in 24 h	% Animals showing histomorphological changes			
				Stomach	Liver	Heart	Lung
I	DW	10 ml/kg	0.0	0.0	0.0	0.0	0.0
II	VN	1	0.0	0.0	0.0	16.7	0.0
III	VN	1.5	0.0	0.0	0.0	33.3	0.0
IV	VN	2	0.0	0.0	0.0	33.3	0.0
V	VN	2.5	0.0	0.0	16.7	50.0*	0.0
VI	VN	5	33.3	0.0	33.3	50.0*	0.0
VII	VN	7.5	50.0	0.0	50.0*	66.7†	33.3
VIII	VN	10	66.7	0.0	50.0*	66.7†	66.7†

n = 6 in each group. VN: *Vitex negundo* extract, DW: Distilled water. *$P<0.05$, †$P<0.01$ when compared to Group I using Z test

in 7.5 and 10 g/kg, wt. doses of VN extract, microscopically. Histomorphological changes were observed in the liver with intermediate and higher doses. Although the specimens of the liver appeared apparently normal on gross examination, they showed non-specific portal dilatation significantly *($P<0.05$)* in doses of 7.5 and 10 g/kg, wt. of the extract, microscopically. Whereas changes in the lung was observed with a higher dose (10 g/kg, wt.) only. The lungs showed edema and congestion on gross examination and significant *($P<0.01$)* vascular dilatation and congestion microscopically. From the histomorphological examination it seems that the major toxic assault of VN was on the heart. The major cause of mortality seems to be cardiopulmonary arrest as non-reversible severe dyspnoea was noticed mostly after twelve hours of the administration of the extract. This occurred in only those animals from various groups in which mortality was observed. The appearance of dyspnoea could not have been due to lung injury as a toxic change in the lung was seen only in a higher dose of VN extract. Therefore, the dyspnoea is likely to have been caused by cardiac toxicity in the form of vascular dilatation and hemorrhage which seems to be major cause of mortality in the present study.

Acknowledgements

The authors are grateful to Dr. N. Gagnae (Professor, Department of Pathology, MGIMS, Sevagram (Wardha), Maharashtra for helping us to undertake histopathological work in the department for the present study.

V. Tandon,* R. K. Gupta

*Post Graduate Department of Pharmacology & Therapeutics, GMC, Jammu (J&K) - 180001, India;
Department of Pharmacology, M.G.I.M.S. (Sevagram), Wardha, Maharashtra. India.
E-mail: dr_vishaltandon@yahoo.com

References

1. Telang RS, Chatterjee S, Varshneya C. Studies on analgesic and antiinflammatory activities of *Vitex negundo* Linn. Indian J Pharamacol 1999;31:363-6.
2. Ravishankar B, Bhaskaran NR, Sasikala CK. Pharmacological evaluation of *Vitex negundo* (Nirgundi) leaves. Bull Med Ethano Biol Res 1985;6:72-92.
3. Ghosh MN. Fundamentals of experimental pharmacology. 2nd ed. Calcutta: Scientific book agency; 1984.
4. Morrow JD, Roberts II LJ. Lipid-derived autocoids eicosonoide and platelet-activating factor. In: Hardman JG, Limbird LE, Gilman AG, editors. Goodman Gillman's. The pharmacological basis of therapeutics. 10th ed. New York: Mcgraw Hill; 2001. p. 669-85.

Influence of sodium curcuminate on castor oil-induced diarrhea in rats

Sir,

The rhizome of *Curcuma longa* Linn. (turmeric) is widely used in the Indian system of medicine. Curcumin (diferuloyl methane) isolated from the alcoholic extract of turmeric has been shown to be a potent antiinflammatory agent.[1] The sodium salt of curcumin was found to be more effective in inhibiting carrageenin-induced rat hind paw edema when compared with curcumin and some of its semi-synthetic analogues.[2] It has also been reported that sodium curcuminate decreased the resting tone of rabbit intestine and reversibly inhibited contractions induced by nicotine, acetylcholine, 5-hydroxy tryptamine, histamine and barium chloride on isolated guinea pig ileum.[3] Drugs possessing antiinflammatory activity have been shown to delay castor oil-induced diarrhea, suggesting the involvement of prostaglandins in this mechanism.[4] The antiinflammatory action of sodium curcuminate is not fully understood. Therefore, the present study was designed to investigate the mechanism that might account for the antiinflammatory action of sodium curcuminate by castor oil-induced diarrhea in rats.

The sodium salt of curcumin (Loba chemie) was prepared as described earlier[1] and used in the study. The experimental study was approved by the Institutional Animal Ethics Committee. A modification of the method of Awounters *et al.*[4] was followed. In this study, Albino rats (Wistar) of either sex (200-260 g) were fasted for 18 h and water was provided *ad libitum*. The animals were divided into six groups of six animals each. Sodium curcuminate was administered (0.1, 0.2, 0.6 and 1 mg/kg) orally to the first four groups. The fifth group received the standard antiinflammatory agent, indomethacin (10 mg/kg, *i.p.*) and the sixth group water (vehicle control).

One hour after treatment, each animal received 1 ml of castor oil (CDH, Mumbai) orally by gavage and was then observed for defecation. The rats were observed over a 4 h period for the assessment of characteristic diarrhea droppings in the transparent plastic dishes placed beneath the individual rat cages.

The data were analyzed by one-way analysis of variance, followed by Dunnett's test and $P<0.05$ was considered significant. Administration of castor oil produced characteristic semisolid diarrhea droppings in 18 h starved rats of the control group during the 4 h observation period (Table 1). Sodium curcuminate dose-dependently inhibited the occurrence of diarrhea as compared to the vehicle-treated control rats. The highest dose of sodium curcuminate (1 mg/kg) significantly inhibited castor oil-induced diarrhea with the percentage inhibition of 80.03, which was comparable to that of indomethacin (10 mg/kg).

Table 1

Effect of sodium curcuminate on castor oil-induced diarrhea in rats

Drug per kg, b.w. at 0 h+ castor oil 1 ml, p.o., at 1 h*	*Mean number of wet faeces*	*% Inhibition*
Control (Water, 5 ml)	6.66 ± 0.71	–
Indomethacin (10 mg)	0.66 ± 0.33 †	90.09
Sodium curcuminate (0.1 mg)	4.16 ± 0.47 †	37.53
Sodium curcuminate (0.2 mg)	3.50 ± 0.49 †	47.45
Sodium curcuminate (0.6 mg)	2.16 ± 0.60 †	67.56
Sodium curcuminate (1 mg)	1.33 ± 0.55 †	80.03

*The test drug and vehicle were given *p.o.* and indomethacin was given *i.p.*, Values are mean±SEM, $n = 6$ in each group. †$P < 0.001$ when compared to control

The delay of castor oil-induced diarrhea has been demonstrated to characterize non-steroidal antiinflammatory drugs (NSAIDs). Awounters *et al*[4] tested 44 NSAIDs and found that the selective potencies of the drugs in castor oil-induced diarrhea and in the carrageenin-induced test correlated well. The sodium curcuminate was found to be more effective in inhibiting carrageenin-induced rat paw edema when compared with curcumin and some of its semisynthetic analogues.[2]

The delay of castor oil-induced diarrhea and the inhibition of carrageenin induced inflammation by sodium curcuminate may be related to the inhibition of prostaglandin synthesis.

In earlier studies, sodium curcuminate has been shown to antagonize the contractions of isolated guinea pig ileum induced by various agonists.[3] This property is also shared by most of the NSAIDs.[5] The inherent resting tone of the intestinal smooth muscle is known to be maintained by continuous intramural generation of prostaglandins and the inhibition of prostaglandin biosynthesis by NSAIDs results in decrease of the resting tone.[6] Sodium curcuminate has been shown to produce a similar decrease in the resting tone of rabbit intestine.[3]

Hence, it may be quite possible that all these activities could be attributed, at least partly, to inhibition of prostaglandin biosynthesis. However, further studies are required to understand the mechanism that might account for the antiinflammatory and related action of sodium curcuminate.

N. Gnanasekar, J. B. Perianayagam*
Department of Pharmacology, K. P. College of Pharmacy, Thiruvannamalai, India; *Faculty of Pharmaceutical Sciences, Guru Jambheshwar University, Hisar, India.
E-mail: jamesjbp@rediffmail.com

References

1. Ghatak N, Basu N. Sodium curcuminate as an effective antiinflammatory agent. Indian J Exp Biol 1972;10:235.
2. Mukhopadhyay A, Basu N, Ghatak N, Singh KP, Gujral PK. Structure activity relationship with respect to antiinflammatory activity in a series of curcumin analogues. Proc Int Union Physiol Sci 1974. Vol XI. p. 241.
3. Rao TS, Basu N, Siddiqui HH. Antiinflammatory activity of curcumin analogues. Indian J Med Res 1982;75:574-8.
4. Awounters F, Niemegeers CJ, Lenaerts FM, Janssen PA. Delay of castor oil diarrhoea in rats: A new way to evaluate inhibitors of prostoglandin biosynthesis. J Pharm Pharmacol 1978;30:41-5.
5. Famaey JP, Fontaine J, Reuse J. The effects of non-steroidal antiinflammatory drugs on cholinergic and histamine-induced contractions of guinea pig isolated ileum. Br J Pharmacol 1977;60:165-71.
6. Ferreira SH, Herman A, Vane JR. Prostaglandin generation maintains the smooth muscle tone of the rabbit isolated jejunum. Br J Pharmacol 1972;44: 328-9.

Therapeutic substitution: A hidden irrationality

Sir,

It cannot be denied that irrationality is widely prevalent in the field of medicine. Doctors with wrong practices, pharmaceutical companies with their promotional tactics, patients indulging in self-medication and the government's inability in implementing an effective and efficient drug control system are some of the known apparent factors responsible for irrational drug therapy. But one of the serious factors on the part of the pharmacist is drug substitution, which still remains hidden and can contribute significantly to the irrationality. When a prescription is written for a proprietary product, the pharmacists must, under the law, dispense that product only, unless they persuade the doctor to alter the prescription. Under such circumstances they can substitute a generic product for the proprietary formulation prescribed by the doctor (*Generic Substitution*[1]). But indulging in *therapeutic substitution* is a serious irrationality on the part of the pharmacists where a drug belonging to same class but with a different chemical structure is deemed to be pharmacologically and therapeutically equivalent and is used as a substitute.[1] This can cause serious adverse therapeutic outcomes and therapeutic failures. This also denies the doctors' right to prescribe their priority drug for a given indication as well as denies the patients' right to have chemically same drug prescribed by a doctor. Therefore, it also has legal implications.

Drug substitution is done quite often by the pharmacist and studies had not been carried out on this aspect in the past. Therefore, a prospective study was carried out by collecting 200 prescriptions from patients/relatives who, after attending the OPDs of different departments, had visited different chemist shops near the Government Medical College, Jammu to purchase prescribed drugs. The prescribed drugs in the prescriptions were compared with the actual drugs received by the patients/relatives from the chemist shops for evaluating the total drug substitutions, generic substitutions and therapeutic substitutions in the prescriptions. The incidence of each group of drugs in prescriptions showing generic substitution and therapeutic substitution was also worked out. The present study was irrespective of the total number of drugs substituted in one prescription and the number of visits of patients/relatives. An interview or questionnaire study of the patients/relatives and chemists to ascertain the cause of drug substitution was not done as diverse answers and reactions were expected. Moreover, lack of cooperation on the part of the chemists interfering with the outcome of study was feared. Doctor-patient interactions were also not studied; the present study concentrated only on therapeutic transactions.