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Letter to the editor

Azelastine: well known ciliotoxic agent?

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In a recent in vitro study, Su et al. claimed that chlorbutol, xylometazoline, azelastine and lignocaine are 'known to be ciliotoxic' and used them as reference ciliotoxic compounds (Su et al., 1995). This should be taken with caution because in vitro studies have been therapeutically relevant by revealing nasal ciliodepressing actions of potent ciliotoxic agents, such as mercurial or lipophilic (chlorbutol) preservatives (Van de Donk et al., 1981, 1982; Batts et al., 1990) or inhalation anesthetics (Hermens and Merkus, 1987). Conversely, other in vitro toxic data concerning less cilioactive agents such as the polar preservative benzalkonium chloride (Van de Donk et al., 1981, 1982; Batts et al., 1990; Ainge et al., 1994; Braat et al., 1995), the long-acting alpha sympathomimetic agent xylometazoline (Bos and Jongkees, 1966; Van de Donk et al., 1981) or antihistamines (Van de Donk et al., 1981; Fukuda et al., 1984; Karttunen et al., 1990; Merkus and Schüsler-van Hees, 1992) have frequently given rise to controversy and seem of less therapeutic value. Moreover, the case of the H_1-antagonist azelastine is surprising because most experimental and all clinical evidence show that azelastine improves mucociliary transport function.

1. Azelastine and ciliary beat frequency in vitro

The effect of azelastine on mucociliary transport function has been extensively studied by Achterrath-Tuckermann et al., 1992, using several pharmacological models, both in vitro and in vivo. In vitro, ciliary beat frequency (CBF) was investigated by using human airway mucosal samples. The obtained results showed that azelastine was unable to modify CBF in vitro (Achterrath-Tuckermann et al., 1992).

In contrast with Achterrath-Tuckermann et al., 1992, Su and Li Wan Po, 1993 have recently reported that azelastine nasal spray inhibits ciliary beat frequency in an in vitro rat tracheal cilial model. The article of Achterrath-Tuckermann et al., 1992 was previous to that of Su and Li Wan Po, 1993. However, these latter have not given a single comment or explanation for the remarkable difference of the results. A careful examination of Tables and Figures shows that Achterrath-Tuckermann et al., 1992 have used a maximal dose of 100 μM of azelastine, while Su and Li Wan Po only found inhibition of CBF at concentrations higher than 125 μM. At first sight, this point may thus explain the discrepant results, i.e. azelastine concentrations higher than 100 μM should be

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required to observe CBF inhibition. However, other potential factors may also explain the differences: (i) Achterrath-Tuckermann et al., 1992 have used human tissue, while Su and Li Wan Po used a rat model and (ii) Achterrath-Tuckermann et al., 1992 used pure azelastine compound and Su and Li Wan Po used the nasal spray containing benzalkonium chloride as preservative (see below).

A third in vitro study dealing with azelastine and CBF is that of Tamaoki et al., 1993. These authors investigated the effect of azelastine on airway mucociliary transport function by measuring ciliary motility of human bronchial epithelium in vitro with a photoelectric method (Tamaoki et al., 1993). Again, the results of Tamaoki et al. contrasted with those of Su and Li Wan Po, i.e. azelastine was unable to inhibit ciliary beat frequency (Tamaoki et al., 1993). More importantly, azelastine slightly stimulated ciliary beat frequency, even at concentrations of 1000 μM (Tamaoki et al., 1993). This slight stimulation was substantiated by a parallel increase in cyclic AMP, an agent previously reported to mediate cilioexcitation (Hermens and Merkus, 1987).

As Batts et al. pointed out (1990), some controversial results may be explained by differences in species sensitivity. Thus, benzalkonium chloride seems to depress ciliary beating in human, guinea-pig and frog tissue but not in rabbit and chicken embryo tissue (Batts et al., 1990). Therefore, the above differences in the results may be explained if one assumes that azelastine depresses ciliary beating in rat but not in human tissue. Or that benzalkonium chloride depresses ciliary beating in rat tissue.

2. Azelastine and mucociliary transport function in animal models

Achterrath-Tuckermann et al., 1992 investigated the effect of azelastine on CBF in vivo using anesthetized guinea pigs. Azelastine, given i.v. up to a dose of 2 mg/kg, was unable to depress CBF in vivo. Moreover, azelastine p.o. increased the tracheal output of phenol red in mice. Finally, i.v. azelastine dose-dependently enhanced mucociliary clearance measured by elimination of ^{99m}Tc-labeled erythrocytes in rabbits. The authors concluded that azelastine increases the mucociliary clearance by enhancing bronchial secretion.

The above results suggest that azelastine is not ciliotoxic in vivo. However, in these animal studies azelastine was given intravenously or intragastrically. Therefore, we cannot exclude a local inhibition of CFB by the nasal spray in vivo.

3. Azelastine nasal spray and mucociliary transport function in humans

Pasali and Piragine, 1994 performed a comparative study of azelastine nasal spray (0.14 mg/nostril twice daily = 0.56 mg/day) vs. cetirizine tablets (10 mg once daily) in patients with perennial allergic rhinitis. The authors included a total of 40 patients who where treated for 8 weeks. Nasal mucus transport time (NMTT) was investigated with the aid of a non-absorbable tracer (Pasali and Piragine, 1994).

Pasali and Piragine found that mucociliary clearance rates improved gradually but faster and with greater relevance in the azelastine group than in the cetirizine group. Thus after 8 weeks of treatment, azelastine reduced NMTT from 22–23 min to 15–16 min, while cetirizine reduced it to 19–20 min. Improvements in both groups were significant ($P < 0.001$ for azelastine and $P < 0.01$ for cetirizine) (Pasali and Piragine, 1994).

Recently, Klimek and Mosges, 1995 confirmed the above results in patients with seasonal and perennial allergic rhinitis by using the sacharine-dye test. NMTT was significantly longer in patients with allergic rhinitis and azelastine nasal spray was found to partially reverse this abnormality (Klimek and Mosges, 1995).

Finally, it is interesting to mention that the H_1 antagonist levocabastine, a compound similar to azelastine, was unable to significantly modify MTT after intranasal administration in human volunteers (Merkus and Schüsler-van Hees, 1992).

Taking together, the above results suggest that the improvement of mucociliary transport function by azelastine nasal spray can be explained by a recovery of normal ciliary function after treatment of the disease.

In conclusion, the results of Su and Li Wan Po, 1993 showing that azelastine exerts a ciliotoxic action in rat trachea in vitro were not confirmed by two other independent studies using human tissue in vitro (Achterrath-Tuckermann et al., 1992; Tamaoki et al., 1993). Moreover, azelastine was unable to induce in vivo ciliotoxic actions in guinea pigs, mice and rabbits (Achterrath-Tuckermann et al., 1992). Finally, in patients with seasonal and perennial allergic rhinitis, azelastine nasal spray gradually improved nasal mucociliary clearance rates (Pasali and Piragine, 1994; Klimek and Mosges, 1995). This beneficial action of azelastine can be explained by a recovery of normal ciliary function after treatment of the disease (Klimek and Mosges, 1995).

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