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New route for Tizanidine administration: a pharmacokinetics and light microscope autoradiography study

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Spasticity could represent a complication of several central nervous system (CNS) disorders. Multiple sclerosis and painful paroxysmal syndromes (e.g. trigeminal neuralgia) are pathologies in which anti-spastic drugs are used to a greater extent . Baclofen, tizanidine (TIZ), benzodiazepines, dantrolene, and, more recently, gabapentin are the pharmacological agents more widely used. Baclofen, TIZ, benzodiazepines, gabapentin, clonidine but not dantrolene are active on CNS. The alpha2 adrenoceptor agonist TIZ is one of the most effective and largely used anti-spastic drugs. Oral treatment is the only route of anti-spastics administration, although it may cause problems of bioavailability and/or compliance in spastic patients with impaired deglutition. This study was designed to assess the possibility of develop a new route of administration of TIZ and to identify its targets in the spinal cord.

New Zealand rabbits were treated with oral (OR , n=6), intramuscular (IM, n=6) or intranasal (IN, n=6) TIZ (3.2 mg/kg/day). Plasma concentration was measured by HPLC on samples collected at 0, 30, 60, 90, 120 and 480 min after treatment. Curves of average concentrations of TIZ vs. time were constructed. In plasma, TIZ reached a peak between 45-65 min after administration. C_{max} was in the range of 268.33–1213.64 ng/ml for IM treatment, of 73.95–135.92 ng/ml for IN treatment and of 16.86–857.25 ng/ml for OR treatment. After pharmacokinetic studies, different spinal cord tracts were removed and used for radioligand binding assay and autoradiography. Using [3H]-RX821002 ([3H]-RX) (0.1-14nM), the Kd and Bmax for every spinal cord segment were calculated. The non-specific binding was obtained with 100μM of (-)-epinephrine. [3H]-RX sites were accumulated in the superficial laminae of dorsal horn. Dense [3H]-RX binding in control was seen over the superficial dorsal horn (laminae I-II) and centrally located lamina X. The ventral horn showed moderate levels of binding. [3H]-RX was displaced after TIZ treatment using different administration routes. The heaviest accumulation of silver grains (lowest displacement of TIZ) occurred after OR administration of the compound, the lowest after IM administration. These results suggest that both IM and IN administration of TIZ may represent routes of administration of the drug alternative to the OR one.

Considering predictable adverse effects of IM treatment, the IN administration could represent the elective route to administrate this kind of drugs.

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