

132

Authors: B. Averbeck, M. Braeter*, U. Ravens

Institution: Institute of Pharmacology & Toxicology, Medical Faculty, Dresden University of Technology;
* APOGEPHA Arzneimittel GmbH Dresden

Title: EFFECTS OF SPASMOLYTIC DRUGS ON ISOLATED PIG DETRUSOR MUSCLE:
COMPARISON OF OXYBUTYNIN, TOLTERODINE, AND PROPIVERINE

Aims of Study:

Although urinary incontinence is a common problem in the ageing population, selective drug therapy is not yet achieved because of complex receptor responses in the urinary bladder. Drugs that modulate cholinergic receptors are considered to be therapeutically effective. There is still a need for more efficient drugs to be developed. Screening new agents for the purpose of development of new drugs requires animal models in which the in-vivo and in-vitro responses are comparable to those in human bladder. As in human bladder, detrusor contraction in pig is predominantly regulated by a cholinergic mechanism. The aim of our study was to investigate the effects of propiverine on electrically stimulated strips of detrusor smooth muscle. The anticholinergic drugs oxybutynin, tolterodine, and atropine were used for comparative purposes.

Methods:

The muscle strips were mounted in organ baths containing oxygenated Tyrode's solution. After two 10 min periods of exposure to carbachol (1 μ M) followed by 30 min of re-stabilisation, the muscles were stimulated electrically (stimulation parameters: amplitude 60-80 mA, duration 5 s, frequency 30 Hz) and drugs were added in a cumulative manner beginning at 10^{-10} mol/l for atropine (10^{-9} mol/l for the other agents) and increasing in steps of one log unit. At the end of each experiment, the muscles were exposed to tetrodotoxin (1 μ M) in order to block nerve conduction. A sigmoidal dose-response curve was fitted to the data (GraphPad Prism).

Results:

All drugs attenuated the contractions induced by electrical field stimulation (EFS) in a concentration-dependent manner. With exception of atropine, maximum inhibition of EFS-induced contractions was between 88 and 92% and was obtained at 10^{-3} mol/l. The respective values for atropine were 79 % at 10^{-5} mol/l. Tetrodotoxin further decreased the amplitudes of EFS-induced contractions to 15 % (atropine), 4 % (propiverine) and 2 % (tolterodine, oxybutynin) of pre-drug control revealing a non-cholinergic mechanism of muscle contraction. The differences in responses between atropine and the other drugs correspond to an atropine-resistant part of bladder contractility. Comparing the IC_{50} values the following order resulted (95 % confidence interval; μ mol/l): propiverine 16.5 (6.9 - 39.6) \geq oxybutynin 5.5 (2.7 - 11.0) = tolterodine 4.8 (1.8 - 12.7) $>$ atropine 0.012 (0.006 - 0.022). The Hill coefficient for tolterodine and oxybutynin was < 1 implying more than one site of action involved.

Conclusions:

As expected, atropine reduced only about 80 % of bladder contractility after EFS. From the similar IC_{50}

values for propiverine, tolterodine and oxybutynin it is concluded that they have comparable antagonistic effects in this model which is consistent with their in-vivo effects in mini-pigs (1). However, tolterodine and oxybutynin seem to be markedly different from the mode of action of atropine. This is in contrast to published data on tolterodine where a simple competitive blockade of bladder cholinergic receptors was postulated (2). On the other hand, according to published data propiverine was shown to affect cholinergic receptors and additionally possess a directly muscle-relaxing effect (3).

EFS-induced contractions in porcine urinary bladder muscle strips are a reliable model to screen for drugs affecting bladder contractility. The drug effects can be confirmed in a validated *in-vivo* model of the same species.

References:

(1) Scheepe JR, Braun PM, Bross S, Weiss J, Zandler S, Gramatté T, Alken P, Jünemann KP. 2000. A standardised model for in-vivo investigations of anticholinergic effects on bladder function, salivation and electromyographic characteristics of the detrusor. *Akt Urol* 31:311-316.

(2) Nilvebrant L, Andersson KE, Gillberg, PG, Stahl M, Sparf B. 1997. Tolterodine – a new bladder selective antimuscarinic agent. *Eur J Pharmacol* 327:195-207.

(3) Kaneko S, Nakano D, Ohara M, Nishimori T. 1999. Effects of propiverine hydrochloride (propiverine) on isolated rat and dog urinary bladder. *Folia Pharmacologica Japonica* 113:145-156.