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Impact of MDR1 polymorphisms on the analgesic efficacy of tramadol in patients after minor surgery

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BACKGROUND

- Pharmacokinetics and efficacy of tramadol displays high interindividual variability where genetic polymorphism have been shown to contribute in part to drug efficacy and safety.
- P-glycoprotein is a transmembrane transporter influencing pharmacokinetics of xenobiotics, including bioavailibility of drugs such tramadol and other opioids.
- P-gp is coded by the ATP-binding cassette sub-family B multi-drug resistance gene MDR-1.
- Among the 50 single nucleotide polymorphisms (SNP) of the MDR1 gene, more attention has been focused on SNP at position 3435 in exon 26.
- Homozygous with both mutant allels (TT) were associated with more than two folder lower intestinal expression of P-gp → higher drug disposition to the brain → better efficacy of tramadol, but also higher sensitivity to adverse effects.

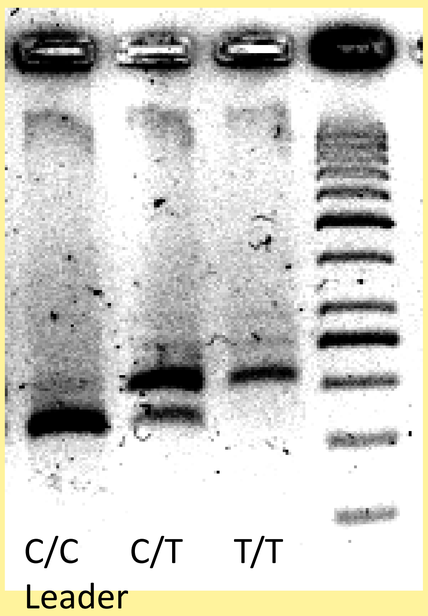
⇨ PURPOSE OF OUR STUDY

- to evaluate possible impact of MDR1 polymorphisms on the analgesic efficacy of tramadol in realistic clinical settings with patiens after a minor surgery.

MATERIALS AND METHODS

Totally 156 patients after minor surgery were enrolled in the study. Each of the subjects gave written informed consent. Venous blood (7ml) was obtained and DNA was isolated by using QIAamp DNA Blood Mini Kit (Quiagen Ltd.). The genotypes were determined using a polymerase chain reaction-based restriction fragment length polymorphism (PCR-RFLP) analysis. Restriction by enzyme Bsp1431 produced DNA fragments that were separated on 3,5% agarose gel and visualized after ethidium bromide staining (Figure 1). Pain intensity was assessed using visual analogue scale at 2 and 24 hours after minor surgery.

Figure1.: Agarose gel of the PCR fragments. The polymorphisms in exon 26 are shown.



RESULTS

Variant allele 3435T was seen in frequency of 58.3%. There were no statistically significant differences between MDR1 subgroups in basic demographic parameters. Table 1 shows mean VAS2h, mean pain difference, defined as VAS2-24h and mean tramadol consumption in groups C3435CC, C3435CT and C3435TT. There were no significant differences in the drug consumption, reporting of adverse reactions or need for rescue analgesic medication among the MDR1 genotype subgroups.

Table 1.: Comparison of pain characteristics and tramadol consumption in MDR1 genotype subgroup over 24 hours postoperative period. Data are presented as mean ± S.D.

Gene	Predicted genotype	Initial pain intensity VAS2h (mm)	Pain difference VAS2-24h (mm)	Total tramadol consumption (mg/kg/24h)
MDR	3435CC (n=22)	40.0 ± 11.8	19.3 ± 12.1	2.62 ± 1.1
	3435CT (n=86)	43.2 ± 17.9	21.3 ± 14.6	2.42 ± 1.1
	3435TT (n=48)	**45.5 ± 16.1**	**23.4 ± 15.4**	**2.44 ± 1.3**

CONCLUSIONS

- There were approximately 20% higher mean pain difference values in the 3435TT group in comparison with the wild type subjects, which reflects the best efficacy of tramadol at the group of homozygous with both mutant allels (TT). However, our results did not reach statistical significance.
- Further studies of the the other SNPs of P-gp as 2677G>T/A, 1236C>T and the haplotypes between different SNPs should be done.

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