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Co-mobilization of quaternary ammonium compounds and antibiotic resistance genes among bacteria - a matter of concern?

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Diverse environmental stressors (e.g. biocides) can participate in the selection and maintenance of antibiotic resistant (ABR) strains and/or genetic elements. Quaternary ammonium compounds (QACs) are heavily used in hospitals, industry and household products. Our goal was to assess the spread of known QACs resistance genes occurring in Gram-positive/Gram-negative bacteria among Enterococcus spp from several sources, and to evaluate if the genetic elements linked to their mobilization also carry ABR genes.

We analyzed 120 E. faecalis, 176 E. faecium and 104 Enterococcus spp from hospitalized (82) or healthy humans (43), piggyfer environments/swine (17), aquaculture/traut (29) and sewage (47) (Portugal, 1997-2012). Susceptibility to AB was studied by disk diffusion/micro dilution and to benzalkonium chloride (BC) by microdilution methods. Genes codifying resistance to AB (vanA, vanB, tetL, intK, ermB, aac(6’)-Ile-aph(3’)-Ia, aadA, bllZ, qacB) or QACs (qacA, qacH) sequences, qacEA1, qacGL, qacE primary and the link of IS1216 to qac genes were searched by PCR.

Mating assays, MLST and analysis of the plasmid carrying qac genes (ST174-PFGE, rep/rep typing) were done.

A ST17 E. faecalis strain (ampicillin, tetracycline, erythromycin, HLR-gentamicin/streptomycin resistant, BZ MRC=Resist) from hospital sewage carried the qacB gene previously identified in Staphylococcus spp and E. faecalis V583 (GenBank Y16945.1, AE016833.1). This gene was located in a 50Kb plasmid also carrying a partial fragment of CTn900 containing tet(B) as well as tetM, aac(6’)-Ile-aph(3’)-Ia, aadA, and rep/repB25 genes. Two copies of IS1216 linked a 3000bp region including qacH. This qacH plasmid was transferred to E. faecium BM4103F using different AB as selective agents and transconjugants (n=4) were resistant to tetracycline, HLR-gentamicin, HLR-streptomycin (n=4) and erythromycin (n=2). Plasmids of variable size contained other AB genes (ermB and aadA-3000kb).

This is the first description of qacH in E. faecium which seems to be located in a composite IS1216 transposon. The use of both biocides and AB might favour the spread and/or persistence of genetic elements carrying genes for resistance to several selective agents often used in different settings. The results also demonstrate the high genome plasticity of E. faecium clones to acquire different adaptive traits.

COMT GENETIC POLYMORPHISMS MAY INFLUENCE OPIOID DOSE REQUIREMENTS IN THE TREATMENT OF CANCER-RELATED PAIN

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Opioid analogues are the mainstay treatment for moderate to severe cancer-related pain. However, clinical studies suggest that genetic variability may result in significant differences in analgesic response to opioids. The μ-opioid receptor (OPRM1) is the primary site of action for opioids. The polymorphism A118G is relatively frequent in Caucasians and causes an amino acid change from asparagine to aspartic acid. This polymorphism seems to influence opioids action, with homozygous for A allele requiring lower doses of opioids. Catabolism-O- methyltransferase (COMT) is involved in the metabolism of catecholamines, which have a role in the nociceptive mechanism. The functional polymorphism Val108/158Met codes the substitution of valine (Val) by methionine (Met). Individuals with the Met/Met genotype have the lowest activity of the COMT and have been reported to have increased pain sensitivity and lower μ-opioid system activation during sustained pain. Polymorphisms in multidrug resistance protein 1 (MDR1) can have pharmacologic consequences after opioids administration. Two of the most frequent polymorphisms are C3435T and C1236T. Homozygous individuals for T allele of the C3435T have lower mRNA expression. C1236T was found to be in linkage disequilibrium with C3435T and was also related to different opioid doses, higher in T allele homozygous. Our purpose was to investigate the effects of these polymorphisms on several pain-related parameters in Caucasian cancer patients.

DNA samples from 30 cancer patients were genotyped for the polymorphisms in OPRM1 (rs799713), COMT (rs4680), and MDR1 (rs1128503, rs1045642) with Real-Time PCR. Daily doses were re-expressed as oral morphine equivalents. We examined the relation between the polymorphisms and opioid dose, pain intensity, performance status, adverse effects, age, gender, bone or CNS metastases and breakthrough pain.

Total morphine consumption was related to the polymorphism Val108/158Met in COMT gene, with carriers of Met allele showing to be significantly associated with higher dose of opioids (p = 0.004, Pearson χ2-test), which was also confirmed by logistic regression adjustment to age and gender (p = 0.013). All the other polymorphisms and parameters revealed no statistically significant association.

This preliminary result indicates that genetic variation at COMT enzyme may influence opioid dosing requirements in the treatment of cancer-related pain.