research.

284. (130) **OPIOID-ASSOCIATED QT-INTERVAL PROLONGATION: EFFECTIVENESS OF DATA MINING TECHNIQUES OF THE PUBLIC VERSION OF THE FDA ADVERSE EVENT REPORTING SYSTEM (FAERS) FOR EARLY ADVERSE DRUG REACTION SIGNAL IDENTIFICATION.**

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INTRODUCTION: the prolongation of the QT interval is a serious and potentially fatal adverse reaction that has led to the discontinuation of many drugs (including some opioids). Data mining on pharmacovigilance databases can detect signals that identify early the risk associated with some drugs.
OBJECTIVE: To examine the association between opioids and risk of QT prolongation in reports submitted to the US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) between 2004 and 2017.
METHODS: Relevant reports in the FAERS were identified and analyzed. The reporting odds ratio (ROR±IC95), Proportional ADR reporting ratio (PRR±IC95), Chi square (Yates' correction), and Yule's Q (Q±IC95) was used to detect spontaneous report signals, calculated using the case/non-case method. Cases were identified using Standard Medical Querry (SMQ) for QT Prolongation defined by MedDRA 21.0 in which opiods (Meperidine, Tramadol, Dextropropoxyphene, Methadone, Fentanyl, Morphine, Hydromorphone, Oxycodone, Buprenorphine, and/or Nalbuphine) were the suspected drug.
RESULTS: A total of 25885 drug-reaction pairs was found in 445627 opioid reports through 36.389.458 total reports. Significant Signal (ROR, PRR, Chi2, Q) were found for whole opioid group: ROR 1.30 (1.28-1.31), PPR 1.28 (1.27-1.30), Yule's Q 0.13 (0.12-0.14) and Chi2 With Yate's Correction: <0.000001. Analysis of individual opioids show significant signals for QT prolongation for each drug. The temporal evolution of the different signals according to the number of reports included from 2004 to 2017 shows early significant positivization of signals in the first 6 to 12 months.
CONCLUSIONS: Analysis of the FAERS database showed significant signals for QT prolongation with opioid treatments. Underlying mechanism is unknown, but it seems to be linked to hERG channel blocking. Proposed mining shows that statistical signals could warn of this risk in some drugs between 5 to 10 years before data from specific clinical studies, proposing an early tool to minimize adverse reactions.

285. (131) **IN-VITRO CARDIOVASCULAR SAFETY PHARMACOLOGY PROFILE OF TWO GRANULOCYTE COLONY STIMULATING FACTORS (G-CSF).**

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Guideline ICH S7B asks for in vivo and in vitro non-clinical evaluation to determine the arrhythmogenic potential prior marketing authorization of new compounds. For products in the market, such as some recombinant G-CSF, this evaluation is usually incomplete. Consequently, the aim of this work was to evaluate the effects of recombinant G-CSFs for cardiac risk in vitro. Using Langendorff technique, guinea pigs hearts were isolated and arterially perfused. The ECG and the left ventricular developed pressure (LVDP) were constantly recorded. After 50min-stabilization, hearts were exposed to increasing and cumulatively doses of filgrastim and lenograstim (10-30-100-400-800ng/ml), 10 min each. The corrected QT interval was calculated with Bazzet formula and expressed as value in milliseconds against the control (ΔQTc). The LVDP, maximum contraction and relaxation rates (+dP/dT and -dP/dT) were presented as percentage value respect to perfusion without drug. The inhibition of IKr was assessed using an automated patch clamp platform (SyncroPatch 384PE) on CHO cells that stably expressed hERG channels. All cells were recorded in the voltage clamp whole cell mode, in control condition and after the exposure to 800ng/ml of filgrastim. The hERG current amplitude was quantify at the peak tail current elicited by a +40mV pulse followed by a -40mV pulse. The inhibition of hERG current was expressed as percentage of block against the prior control condition. In isolated hearts, only filgrastim showed a significant increase in LVDP (+35 ± 13.3 %, $p<0.05$) and diminished of ΔQTc (-55 ± 6.5 ms, $p<0.05$) at 800 ng/ml. No significant differences regarding control were found in +dP/dT and -dP/dT for both drugs. The SyncroPatch study showed up a non-significant hERG current block after the exposure of a single dose of 800ng/ml of filgrastim. In conclusion, different electrical and mechanical heart behavior between the glycosylated and non-glycosylated form of the G-CSF were observed.

286. (297) **STUDY OF THE EFFECT OF SIRTUINS 1 AND 2 INHIBITORS ON THE SURVIVAL AND MIGRATION OF HEPATOCELLULAR CARCINOMA CELLS UPON SORAFENIB TREATMENT CONDITIONS**

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Sorafenib (SFB) is the only approved drug for hepatocellular carcinoma (HCC) treatment but it only prolongs patients' median survival by nearly 3 months. The main reason underlying the impaired sensitivity to SFB is the multidrug resistance (MDR). Sirtuins 1 and 2 (SIRTs1/2) are overexpressed in HCC and are associated with tumoral progression and MDR. Nowadays there is no second-line treatment for patients who fail to respond to SFB therapy. Aim: to analyze whether SIRTs1/2 activities blockage overcomes MDR during SFB treatment. Methods: HepG2 and Huh7 cells were treated for 72 h with SFB (2 μM) in presence or absence of the SIRTs1/2 inhibitors cambinol (Camb, 50 μM) or EX-527 (EX, 20 μM). Cell survival (2D culture: MTT, clonogenic assay, Annexin V-IP; 3D culture: spheroid growth delay and acid phosphatase assays) and migration (2D: wound healing; 3D: spheroid migration assay) were assayed. Results: In 2D cultures, cells treated with SFB and SIRTs1/2 inhibitors showed a greater fall in cellular viability (Huh7: SBF -24%*, SFB+CAMB -62%*#, SBF+EX -52%*#; **), number of colonies and cellular migration compared to cells treated with SFB alone. In the same way, cells treated with SFB and SIRTs1/2 inhibitors presented with more apoptosis than cells treated with SFB alone (Huh7: SBF +202%*, SFB+CAMB +337%*#, SBF+EX +306%*#; **). In 3D cultures, treatment with SFB and SIRTs1/2 inhibitors significantly diminished spheroid growth (volume), viability and migration compared to SFB treatment. 3D culture was less sensitive to drugs than 2D culture. *$p<0.05$ vs. control; #$p<0.05$ vs. SFB. **HepG2 cells behaved in a similar fashion manner. Conclusions: cambinol and EX-527 exacerbated the effects of sorafenib on cellular survival and migration supporting the potential application of SIRTs1/2 inhibitors in combination with SFB. Results from 3D cultures, that mimic tumor features in vivo, reinforce the clinical relevance of the current data.

287. (334) **ANTI-INFLAMMATORY EFFECT OF MICROPARTICLES CARRYING INDOMETHACIN ON HUMAN RESPIRATORY EPITHELIUM LINE CULTURES**

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