Cytotoxicity of Lidocaine to Articular Chondrocytes:
Changes of Cell Viability and Proteoglycan Metabolism in Vitro
+ Miyazaki, T, Kobayashi, S, Takeno, K, Adam, M, Urban, JPG, Baba H.
+ Faculty of Medical Sciences, The University of Fukui, Fukui, Japan.
+ Dept of Physiology, Anatomy and Genetics, Oxford University, Oxford, UK.

Senior author: mtuyo@u-fukui.ac.jp

Introduction: Pain during activities of daily living is a common presenting complaint of individuals with knee osteoarthritis. Knee pain is also associated with a decrease in quality of life for people with osteoarthritis. Therefore, intra-articular injection of lidocaine is commonly used with hyaluronic acid [1] and/or steroids [2] to relieve knee pain by affected osteoarthritic joints. A lot of studies on the effect of steroids and hyaluronic acid on articular chondrocytes had been done, but many questions on the effect of lidocaine on articular chondrocytes remain unanswered. Lidocaine cytotoxicity to chondrocytes has been implicated in the development of osteoarthritis. This study was performed to determine the effects of varying concentrations and exposure times of lidocaine on the viability and metabolism of bovine articular chondrocytes, in vitro.

Methods: Cartilage was obtained from metacarpal phalangeal joints of 18-24 month bovine. Chondrocytes were isolated by collagenase digestion (1 mg/ml for 18 hours), and encapsulated in alginate beads [3]. Chondrocytes in alginate beads were cultured in DMEM containing 6% foetal calf serum (FCS) at 370 mOsmol at cell densities of 4 million cells/ml. They were then cultured for 24 hours under 21% oxygen with 0.125%, 0.25%, 0.5% and 1% lidocaine, and, without lidocaine as control. These were analyzed in real time, after 1 hour, 12 hours and 24 hours. The cell viability profile across intact beads was determined by manual counting using fluorescent probes (LIVE/DEAD Viability/Cytotoxicity Kit, Molecular Probes) and transmission electron microscope (TEM). Lactate production was measured enzymatically as a marker of energy metabolism [4]. Glycosaminoglycan (GAG) accumulation (as a measure for proteoglycan) was measured using a DMB assay [5].

RESULTS: Cell viability decreased as the concentration of lidocaine increased under conforal microscope (Fig.1A-D). After 24 hours, chondrocyte viability was 95% or higher in the control group, while it was 83.5%, 58.3%, 22.9% and 7.5% in 0.125%, 0.25%, 0.5% and 1% lidocaine concentrations respectively. Under transmission electron microscope, all cells appeared viable in the control group. However, cell death (apoptosis) increased as the concentration of lidocaine increased. In the beads cultured up to 0.25%-lidocaine, cells undergoing apoptosis were seen in the periphery; the cells and nuclei were reduced in size and chromatin condensation was visible in the nuclei (Fig.1E). The rate of lactate production per live cell was significantly higher for cells cultured at 0.5% and 1%-lidocaine than control group and increased with time in culture (Fig.2A). GAG accumulation/tissue volume decreases as the concentration of lidocaine increased (Fig.2B). GAG produced per million cells is greater at 1%-lidocaine (Fig.2C).

DISCUSSION: Lidocaine has been considered a benign and specific sodium channel blocker and it’s widely used as a local anesthetic. However, potency and ratio of effective dose to overdose are important clinical characteristics of anesthetics. In this study, the chondrocyte cytotoxicity of lidocaine is dose and time dependent. High dose lidocaine (up to 0.25%) showed significant chondrocyte death (apoptosis). The cell viability (density) and GAG accumulation/tissue volume decreases with time in culture as the concentration of lidocaine increased. However, with decrease in cell density, the rates of lactate and GAG production per cell increased significantly. These results may occur that the metabolism of survival cells increased in compensation for the increased of cell death induced by the cytotoxicity of lidocaine. Our findings suggest that high dose lidocaine is cytotoxic to articular chondrocytes. Healthy chondrocytes are important for maintenance of the cartilage matrix. Loss of chondrocyte metabolism induced by lidocaine may contribute to cartilage degeneration. Therefore, repeated articular injection of lidocaine potentially worsens osteoarthritis by accelerating cartilage degradation. While these in vitro results cannot be directly extrapolated to the clinical setting, this data suggest caution in prolonged exposure of articular cartilage to high concentration lidocaine.

References.