ARP38

AN AUDIT OF PNEUMOCYSTIS JIROVECI PNEUMONIA IN RHEUMATOLOGY PATIENTS IN THE CANTERBURY REGION OVER A 5 YEAR PERIOD

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Aim: To determine the prevalence of pneumocystis jiroveci pneumonia (PJP) in rheumatology patients prescribed methotrexate or cyclophosphamide by the Christchurch Hospital rheumatology service over a 5 year period.

Methods: The Canterbury Health Laboratory database was searched for rheumatology patients testing positive for PJP from 31 December 2000–31 December 2005. The rheumatology database was then searched to identify patients receiving the same immunosuppressant medication as those who developed PJP to give us the 5 year period prevalence of PJP infection in this patient group.

Results: 3 infected rheumatology patients in the Canterbury region were confirmed. 2 of these patients were women, receiving oral methotrexate for rheumatoid arthritis. The third patient, a man with Wegeners granulomatosis was receiving oral cyclophosphamide. 1050 patients were prescribed methotrexate over the same 5 year period and 53 were treated with cyclophosphamide. Data on demographics, duration of treatment, use of PJP prophylaxis and lymphocyte counts were analysed.

Conclusions: The 5 year period prevalence of PJP in rheumatology patients receiving immunosuppressant treatment with methotrexate or cyclophosphamide was low, despite minimal use of prophylactic treatment. Our results indicate that routine PJP prophylaxis is not required in this patient group.

ARP39

MACROPHAGE MIGRATION INHIBITORY FACTOR MODULATES GLUCOCORTICOID SENSITIVITY VIA EFFECTS ON MAP KINASE PHOSPHATASE-1

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Aim: The requirement for high-dose glucocorticoids (GC) is a major clinical problem in inflammatory diseases. Factors regulating GC-resistance, or impaired GC-sensitivity, are poorly understood. Expression of the pro-inflammatory cytokine macrophage migration inhibitory factor (MIF) is induced by GC, and MIF opposes the actions of GC. We hypothesised that MIF regulates sensitivity to GC.

Methods: Macrophages derived from MIF–/– and wt mice were treated with dexamethasone (DEX) and LPS, and TNF measured by ELISA. MAP kinase phosphatase-1 (MKP-1), I-kappaB and phospho-MAP kinases were measured by western blotting. NF-kappaB activation was also measured by EMSA and a luciferase reporter assay. Protein results were confirmed using real time PCR.

Results: DEX significantly and dose-dependently inhibited LPS-induced TNF in both wt and MIF –/– macrophages, but MIF –/– macrophages demonstrated a 3-fold increase in sensitivity to DEX ($P < 0.0001$). No differences in any parameter of NF-kappaB activation in response to LPS or DEX were detected between wt and MIF –/– cells. In contrast, DEX induced a significant and selective reduction in phospho-p38 MAP kinase in MIF –/– cells which was not observed in wt cells. This was accompanied by significant increased sensitivity to DEX-induced expression of the endogenous MAP kinase inhibitory protein MKP-1 in MIF –/– cells. DEX-induced MKP-1 expression was inhibited by exogenous recombinant MIF.

Conclusions: We have demonstrated that endogenous MIF regulates sensitivity to GC and report a novel mechanism for this observation. Identification of factors regulating GC-sensitivity may allow the development of specific steroid-sparing therapies.

ARP40

INVESTIGATING THE PHARMACOKINETIC AND PHARMACODYNAMIC INTERACTION BETWEEN ALLOPURINOL AND PROBENECID IN HEALTHY SUBJECTS

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Aims: Allopurinol is co-administered with probenecid in patients with gout refractory to monotherapy. However, surprisingly little is known about the benefits of this combination. Therefore, the aims were to investigate the pharmacokinetic and pharmacodynamic interaction between allopurinol and probenecid in healthy subjects.

Methods: Healthy subjects (n = 12) ingested allopurinol (150 mg bd, 7 d), probenecid (500 mg bd, 7 d) and the combination (1-week washout between treatments). Urine and plasma samples were collected at baseline for measurement of urate concentrations. On the 8th day, after fasting overnight, subjects received the respective morning dose of drug(s). Blood and urine samples were collected over 12 h for measurement of oxypurinol and urate concentrations, respectively.

Results: Plasma urate decreased from baseline (mean ± sd, 0.30 ± 0.05 mM) when both allopurinol (0.17 ± 0.06 mM, $p < 0.001$) and probenecid (0.15 ± 0.06 mM; $p < 0.001$) were administered individually. Co-administration caused a further decrease in plasma urate (to 0.09 ± 0.02 mM). Despite the greater effect of the combination on urate concentrations in plasma, co-administration of allopurinol with probenecid substantially (45%) decreased the average steady-state concentration of the active metabolite, oxypurinol (9.4 ± 2.4 mg/L, allopurinol alone; combination, 5.0 ± 1.0 mg/L, $p < 0.001$).

Conclusions: The combination of allopurinol and probenecid had a greater effect on plasma urate than either drug alone, despite plasma oxypurinol concentrations decreasing by almost half when they were co-administered to healthy subjects. Studies in patients with gout are warranted in order to better understand and optimise therapy with this combination.

ARP41

HEALTH-RELATED QUALITY OF LIFE AND PSYCHOLOGICAL DISTRESS DO NOT RETURN TO POPULATION NORMS 12 MONTHS AFTER JOINT REPLACEMENT SURGERY (JRS)

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Aim: People entering a public hospital orthopaedic waiting list for primary JRS had very poor Health-Related Quality of Life (HRQoL) and high psychological distress, compared with the general population. The aim was to compare HRQoL and psychological distress 12 months after total hip or knee replacement with Australian population norms.

Methods: 90 patients who received JRS at the Royal Melbourne Hospital were assessed at entry to the list (baseline) and 12 months post-operatively, using the Assessment of Quality of Life (AQoL) Instrument and K10 Psychological Distress scale. Data were compared with Australian population norms. Pre-operative predictors of 12 month outcome were identified using linear regression. Questionnaires: AQoL: –0.04 (poorest HRQoL) to 1.00 (full HRQoL); K10: 10 (lowest distress) to 50 (highest distress), K10 ≥22 indicates high distress.

Results: Mean (SD) AQoL score increased from 0.40 (0.24) at baseline to 0.57 (0.26) at 12 months, representing large clinically important improvement. HRQoL (mean 0.57, SD 0.26) remained lower than for the overall population (0.83, 0.20) and subgroups aged 60–69 (0.79, 0.19) and 70–79 (0.75, 0.25). Although psychological distress improved after surgery, the prevalence of high distress was 3 times greater than for the population (RR 3.0, 95% CI 2.2 to 4.1). Wellbeing at entry to the list was the strongest predictor of post-operative HRQoL and psychological distress.

Conclusions: While JRS produced large gains in HRQoL, this did not return to population norms at 12 months and high psychological distress remained much more prevalent. Joint replacement surgery is effective, but does not restore full wellbeing.