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Medication use evaluation: Ceftazidime-Avibactam combination therapy compared to ceftazidime-avibactam monotherapy

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Background: The medicinal product Ceftazidime-Avibactam (Zavicefta) is a first-line therapy for the treatment of refractory infections caused by Gram-negative bacilli.

Objectives: The purpose of this study was to evaluate the efficacy and adverse effects of Ceftazidime-Avibactam combined with other antibiotics compared to Ceftazidime-Avibactam monotherapy.

Methods: This retrospective study collected patients who were prescribed the Ceftazidime-Avibactam computer system of a teaching hospital in 2021. The patients were divided into two groups: Ceftazidime-Avibactam combined with other antibiotics (combination therapy) and monotherapy. Their all-cause mortality rates were recorded within 30 days after initiating the treatment. Their clinical cure rates during the test of the cure visit (21 - 25 days after initiating the treatment) were recorded. The cure was defined as the absence of infection-related symptoms and the absence of cultures of the same pathogen. The number of people who required drug treatment due to adverse reactions after drug use were also recorded.

Results: A total of 20 patients were enrolled. There were six patients in the Ceftazidime-Avibactam combination therapy group, of these: one patient died of all causes within 30 days, and two patients were cured 21 - 25 days after treatment.

Discussion: Ceftazidime-Avibactam is mostly prescribed as a monotherapy. There was no statistical difference in the cure rate and all-cause mortality between the two groups. The cure rate was lower than the cure rate data (82 - 85%) in the Zavicefta Taiwan Medical Technology Assessment Report, presumably because the definition of cure in this study is stricter. Fewer patients required medication to deal with its adverse reactions. The limitations of this study were the small sample size and the lack of consideration of complications. Therefore, a large-scale study is needed to further validate these results.

Conclusions: Regardless of the course of Ceftazidime-Avibactam monotherapy or in combination with other antibiotics, there was no statistical difference in all-cause mortality and cure rate among infected patients. Pharmacists should continue to monitor the rationality of last-line antibiotics, engaged in antibiotics stewardship, and tailor advice to best meet individual patient needs and desires.
**A high tacrolimus intra-patient variability is associated with adverse kidney transplant outcomes**

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**Background:** Long-term renal transplantation outcomes are hard to predict, and early prevention of failure of the transplanted kidney is difficult as well. Tacrolimus (Tac) is widely used for the prevention of rejection after renal transplantation. Although the monitoring of Tac concentrations helps to prevent rejection of transplanted kidneys, the long-term outcomes of transplants remains unpredictable. Previous published study results reveal a tacrolimus intra-patient variability (Tac_IPV) in predose tacrolimus concentrations (Tac_CO) is associated with the prognosis of graft function, indicating the higher the IPV, the worse the renal transplantation outcomes.

**Objectives:** Studies related to Tac_IPV are scant in Taiwan, therefore this study aims to investigate retrospectively whether Tac_IPV is associated with either long-term or short-term transplantation outcomes in kidney recipients in a medical centre in Southern Taiwan.

**Methods:** This study collected the patients who underwent kidney transplantation between 1st January 2003 and 31st January 2021 and received regular follow-ups in the outpatient department of the hospital. After reviewing their medical records, those who with Tac_CO records for at least one year and eGFR>25ml/min were enrolled for further analyses. In total, there were 93 patients. Tac_IPV was calculated from predose concentrations measured between seven and 12 months post-transplantation of these patients. Receiver operating characteristic (ROC) methodology was used to distinguish cut point for Tac_IPV. Patients were further divided into two groups, those with high IPV and low IPV, and the correlation of acute and delayed rejection, graft failure and patients death were examined between them. Continuous variables were analysed using t-tests, and categorical variables were analysed using Chi-square tests or Mann-Whitney U tests. Kaplan-Meier survival analyses were used to calculate the cumulative incidence of composite end points in the two groups.

**Results:** The Tac_IPV cut-point obtained by the ROC method was 26%, and patients were furthered divided into two groups: high IPV (> 26%, 38 patients) and low IPV (< 26%, 55 patients). Both of the incidence of acute rejection and late rejection were significantly higher in the patients of high IPV group than in low IPV group (44.7% versus 14.6%, p < 0.05; 21.1% vs. 9.1%, p < 0.05, respectively). The same results for the cumulative incidences at composite endpoints were also found.

**Conclusions:** In this study, higher rates of transplant renal failure, loss of graft function, and patient death were found in the patients with higher Tac_IPV. Acute rejection rate, as one of the indicators for short-term prognoses, was also higher for the patients with higher Tac_IPV. These results were consistent with the previously published data, revealing the feasibility of Tac_IPV as an indicator for both long-term and short-term prognoses of renal transplantation outcomes for Taiwanese recipients. Further studies are warranted to explore the variable factors affecting Tac_IPV.

**Effect of dual trigger on pregnancy outcome in patients with ovarian hyper-response in GnRH antagonist protocol**

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**Keywords:** Dual trigger, GnRH antagonist protocol, Gonadotropin-releasing hormone agonist, Human chorionic gonadotropin

**Objectives:** This study aimed to explore the effect of dual trigger (GnRHa and hCG) on pregnancy outcomes in ovarian hyperresponsive patients with a normal ovarian reserve in GnRH antagonist protocol compared with the hCG-only trigger.

**Methods:** The data of infertile patients who received assisted reproductive technology from 1st January 2018 to 31st December 2020 in the Hospital for Reproductive Medicine Affiliated with Shandong University were retrospectively reviewed. According to the different medication strategies of the trigger, they were divided into two groups: hCG-only trigger group and dual trigger (GnRHa and hCG) group. The general data, the ovulation induction and pregnancy outcomes of the two groups were statistically analysed, and then the effectiveness and safety of the two trigger protocols were compared.
Results: The number of oocytes, the oocytes retrieval rate and the cancellation rate of transfer in the dual trigger group were higher than those in the hCG-only trigger, and the transfer rate of hCG-only trigger group was higher than that in the dual trigger group, and the difference was statistically significant (p < 0.05). There was no significant difference in the number of high-quality embryos, high-quality embryo rate, pregnancy rate, ectopic pregnancy rate, abortion rate, live birth rate and the reasons for the cancellation of transfer cycle between the two groups (p > 0.05).

Conclusions: The pregnancy outcome of dual trigger is similar to the hCG-only trigger, and improves the oocytes retrieval rate. Dual trigger is a relatively effective and safe protocol. Our findings will need to be further validated in well-designed further prospective studies.

Novel tyrosine kinase inhibitor sulfatinib for the treatment of neuroendocrine neoplasms

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Background: Sulfatinib, a novel oral tyrosine kinase inhibitor independently developed in China that selectively targets Vascular endothelial growth factor receptor, Fibroblast growth factor receptor 1 and Colony-stimulating factor 1 receptor kinases, possesses a dual mechanism of anti-angiogenesis and immunomodulatory, thereby generating the synergistic anti-tumour activity. In December 2020 and June 2021, sulfatinib was approved as a monotherapy for unresectable locally advanced or metastatic, well-differentiated extra-pancreatic and pancreatic neuroendocrine neoplasms in China, respectively.

Objectives: This paper mainly reviews the mechanism of action and pharmacodynamics, pharmacokinetics, safety studies and clinical efficacy evaluation of sulfatinib in order to provide theoretical references for the development of new drugs and clinical applications of sulfatinib.

Keywords: sulfatinib; tyrosine kinase inhibitor; neuroendocrine neoplasms

Pharmacy practice of pain management and perioperative nausea and vomiting in thoracic surgery

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Introduction: Based on the practice of clinical pharmacists in thoracic surgery, the problems existing in perioperative pain and post-operation nausea and vomiting (PONV) management were assessed and discussed in a multidisciplinary discussion. Incorporating guidelines and consensus, clinical practice and patient’s wishes into account, the perioperative oligopiate multi-mode analgesia strategy and PONV prevention model were developed.

Objectives: This study aimed to investigate the unreasonable phenomena of perioperative pain management and risk factors of PONV in the thoracic surgery department in the authors’ hospital and conduct the pharmaceutical intervention.

Methods: An observational design was used in this study. Inpatients undergoing thoracoscopic surgery during the perioperative period from December 2020 to February 2021 were selected. The basic information, pain status and PONV that occurred within 24 hours after surgery were collected, the usage of analgesic drugs were summarized and the risk factors of PONV were analysed by univariate analysis and logistics regression analysis.

Results: A total of 140 patients were enrolled, and the incidence of PONV was 37.1%. Univariate analysis showed that PONV was associated with preoperative anxiety state and postoperative opioid use (p < 0.05), and multivariate analysis showed that postoperative opioid use was an independent risk factor for PONV (OR = 3.890, 95%CI (1.560, 9.700), p = 0.004). The medical service organised the departments of thoracic surgery, anaesthesiology and pharmacy to conduct multidisciplinary discussions to take a full range of effective measures. It mainly included: preoperative education and psychological assessment to relieve patients’ anxiety; perioperative oligopiate multi-mode analgesia strategy, such as pregabalin use as preventive analgesia, total intravenous anaesthesia, optimised rehydration strategy, nerve block and epidural infusion, patient-controlled intravenous analgesia without background
Objective: Opioid addiction is a major public health issue, yet its underlying mechanism is still unknown. Several lines of evidence have indicated that ubiquitin-proteasome system (UPS), heat shock proteins and regulators of G protein singling were associated with opioid addiction. The aim of this study was to further explore the roles of UPS, regulator of G protein signalling 4 (RGS4), and heat shock protein 70 (Hsp70) in morphine-induced behavioural sensitisation, an animal model of opioid addiction.

Methods: Combining behavioural and molecular pharmacology and focusing on NAc core, we explored the characteristics of RGS4 and Hsp70 protein expression and poly-ubiquitination in the development of behavioural sensitisation induced by a single morphine exposure in rats, and the effect of a selective proteasome inhibitor, lactacystin, on behavioural sensitisation.

Results: Both poly-ubiquitination expression and Hsp70 expression in NAc core was time- and dose-related increased during the development of behavioural sensitisation, while RGS4 protein expression was not significantly changed during this phase. A second significant finding was that stereotaxic administration of LAC into NAc core could reduce the poly-ubiquitination expression in NAc core, and impair the development of behavioural sensitisation.

Conclusions: The development of behavioural sensitisation was accompanied by poly-ubiquitination and increased expression of Hsp70, while expression of RGS4 was not significantly changed. More importantly, UPS was a positive regulator of the development of behavioural sensitisation. The relationship among UPS, Hsp70 and RGS proteins at the molecular level is worth exploring further.

The result of medication-related problems evaluated by pharmacists at the Mongolian-Japan Hospital, MNUMS

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Keyword: Hospital pharmacy, Personalized and precision medicine, Pharmacy practice research

Background: Errors in medications are one of the main issues which reduce hospital service quality. Routinely patient medication review is intended to prevent medication errors, improve the therapeutic effectiveness and reduce the direct and indirect burden of disease, reducing hospitalisation times and mortality through inpatient medication review. Furthermore, this service engages a multidisciplinary team within the hospital. Developed countries have more emphasised on negative results due to medication errors, in contrast, developing countries rarely focus on a report, or evaluation of medication error. In the authors’ country, there are relatively few studies determining how clinical pharmacists are involved in pharmacotherapy, medication review, and drug safety.

Objectives: This study conducted pharmacist-led patient’s medication review of patients who were admitted to the Mongol-Japan hospital of Mongolian National University of Medical Sciences. In order to achieve this goal to study the medication errors occurred in prescribing medication.

Methods: The retrospective study was carried out among 620 inpatients using the ‘Patient medication review checklist’ for
the period between January to November 2021. The risk severity rate of medication error was classified by the National Coordinating Council for Medication Error Reporting and Prevention Index for categorising medication errors and the classification of PCNE classification for drug-related problems. Statistical testing has been carried out in this study, and results with \( p < 0.05 \) were considered significant.

**Results:** 802 medication errors were detected during the evaluation and 74.9% \( (n = 602) \) were relevant to the prescription step. In the prescription step, 33.8% \( (n = 203) \) of errors were not written correctly due to an international name of medicine, serious drug interactions occurred in 33.7% \( (n = 203) \); 12.6% \( (n = 76) \) were where a wrong dose was prescribed, and for five cases the dose was not adjusted for patients with renal and hepatic impairment (0.7%). Duplicated medicine in a prescription occurred in 1.6% \( (n = 11) \) of cases, contraindication occurred in 1.1% \( (n = 7) \). If classified by the risk rate of total medication error of prescribing step, 51.4% \( (n = 310) \) were ‘near miss’, 46.8% \( (n = 282) \) were ‘mild occasion’. Therefore, the risk factors that lead to medication errors were analysed by binary logistic regression. As result, factors such as age \( (p = 0.01, \text{OR} = 1.01) \), hospital administration day \( (p = 0.00, \text{OR} = 1.22) \), number of administered medicine \( (p = 0.00, \text{OR} = 1.64) \) comorbid diseases \( (p = 0.05, \text{OR} = 1.87) \) folded one-time for probability of medication error. However, gender, type of prescription order (paper or computerized system) are not relevant for the risk factor of medication error. Furthermore, physicians trained in the rational use of medicine are 95% \( (p = 0.01, \text{OR} = 0.05) \) less likely to make prescription errors \( (p = 0.01, \text{OR} = 0.05) \) than non-trained physicians.

**Conclusions:** The majority of medication errors during therapy were rated as ‘near miss’, 39.1% \( (n = 314) \) have mild occasion which means pharmacist can help early detection of medication errors during prescription monitoring and double checking at the dispensing step as well essential for improving safety of medicine and quality of hospital service.

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**Optimisation of medications by pharmacists in the respiratory care ward**

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**Background:** Patients depending on prolonged mechanical ventilators in Taiwan are stepped down in the respiratory care ward (RCW) for further respiratory care. Although these patients are relatively stable with the goal of weaning off ventilators, they may occasionally experience acute symptoms or have multiple underlying comorbidities that require pharmacotherapy. Interventions by pharmacists have always been considered valuable inputs in the patient care process for reducing medication errors, rationalising prescriptions, and lowering the cost of therapies.

**Objectives:** The present study aims to describe the necessary interventions conducted by pharmacists to optimise pharmacotherapy in an RCW of a regional hospital in northern Taiwan.

**Methods:** The retrospective electronic medical records data were obtained for a period of two years (from 2020 to 2021) comprising the patient demographics, medication-related information, and the specific interventions suggested by the pharmacists. The data were evaluated, classified, and submitted for descriptive analysis.

**Results:** A total of 136 pharmacists’ interventions were performed with an acceptance rate of 97.8% in 97 patients. The main interventions include dose adjustment (21.4%), deletion of a drug (19.9%), drug interaction monitoring (19.1%), microbiological culture request (17.6%), the addition of a drug (13.2%), and others (8.8%). Among the adjusted medications, gastrointestinal agents (25%) and glucocorticoids (20.6%) were the most common classes involved, followed by antibiotics (19.1%), cardiovascular agents (14.7%), antiepileptics (13.2%), and others (7.4%). Pharmaceutical interventions showed beneficial in clinical (87.5%), preventive (52.2%) and economic (48.5%) impacts.

**Conclusions:** Other than respiratory care, pharmacists’ interventions appear to provide additional pharmaceutical care for patients admitted to the RCW. These interventions not only improve the clinical outcomes but are also beneficial for preventive and economic impacts.