2294 DRUG-INDUCED TOXICITY AND ITS REVERSIBILITY IN THE REGULATORY NON-CLINICAL STUDIES WITH NEW DRUGS IN JAPAN.

M. Iijima and T. Eimoto. *Clinical Pathology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Aichi, Japan.*

Drug-induced toxicity with therapeutic class and its reversibility were surveyed in more than 150 new drug applications for latest 8 years in Japan. The findings of toxicity consisting of various parameters were examined in repeated-dose toxicity studies, and functional toxicity and reversibility in generative organs were observed in reproduction studies. Further, toxicity profiles between adult and juvenile animals were comparatively analyzed. Most of toxicity findings were well recovered after one- to three-month withdrawal period in rodent and non-rodent species. Irreversible and delayed reversibility findings were recognized in histopathological examination. Liver and kidneys were major targets, although gastrointestinal tract, heart, eye, brain, bone, muscle and reproductive organs were involved. The changes included swelling, degeneration, atrophy, metaplasia, necrosis, fibrosis, calcification, proliferation and others. There was a tendency to delayed reversibility of findings due to the hormonal effects, immunological responses and/or multi-organ lesions. In juvenile animals, the dosage level rather than the targeted profile was a prominent factor in comparison with adult animals.The reversible findings in targeted organs were characterized in the approved drugs.

2295 OPTIMISATION OF PLETHYSMOGRAPHY CONDITIONS FOR USE IN REPEAT DOSE TOXICITY STUDIES.

L. C. Ewart, G. Cullen and J. Valentin. *AstraZeneca, Macclesfield, United Kingdom.*

Barometric whole body plethysmography (WBP) is a non-invasive technique for assessing ventilation. To stabilise the respiratory signal rats, are typically allowed 60 min to settle prior to recording. However, to permit inclusion of WBP into repeat dose studies, conditions that enable rats to settle more quickly (defined as a stable respiratory signal) need to be identified. The objective of this study was to derive these optimal conditions using primarily the respiratory rate measurement. Male Han Wistar rats (weight range 342 to 399g at start of study) were used in a factorial design format. Factors assessed included length of settling time, lighting conditions in the plethysmography room and availability of shade within the plethysmograph (n=4 for each factor). Habituation was also assessed as a consequence of repeated measurements within the same rats. On test days, rats were placed in a plethysmograph (with or without shade) and were allowed 5 or 15 min to settle in either light or dark conditions. Respiratory signals were then recorded for a further 5 min. Rats were tested 8 times over a 26 day period. Respiratory rates were lower in rats that were allowed 15 rather than 5 min to settle (respectively, day –2, 190±22 bpm and 237±16 bpm ($p<0.1$); day 15, 202±11 bpm and 145±10 ($p<0.001$); day 24, 133±14 bpm and 199±16 bpm ($p<0.005$)). Neither the lighting conditions nor the availability of shade had a significant effect on the stabilisation of respiration. Rats also habituated to the plethysmograph with repeated exposure to the plethysmograph study as evident by lower respiratory rates on the last test day. In conclusion, the length of settling time within and habituation to the plethysmograph were the most influential factors. Overall, respiratory rates are higher than those in safety pharmacology studies so to incorporate WBP into repeat dose studies, it would be desirable to habituate animals to the plethysmograph during a pre-study period and have a longer settling time. This would be dependent upon study size but could be achieved by a staggered start.

2296 DETERMINATION OF TIDAL VOLUME AND RESPIRATORY RATE BY PNEUMOTACHOGRAPHY IN THE MARMOSET.

S. Korte[1], B. Schmelting[1] and B. Marshall[2]. *[1]Covance Laboratories GmbH, Muenster, Germany and [2]Covance Laboratories Ltd., Harrogate, United Kingdom.* Sponsor: G. Weinbauer.

Evaluation of respiratory parameters is an essential feature of safety testing. An effective way to evaluate the possibility that a test item might influence respiration is the determination of tidal volume and respiratory rate. The traditional method for measurement of tidal volume in rodents relies on pressure changes in a whole body plethysmograph. Since the marmoset (Callithrix jacchus, 1) is not commonly used in safety pharmacology studies, an alternative method for determination of tidal volume in conjunction with respiratory rate was evaluated. Tidal volume and respiration rate of 16 animals under sedation were determined using a pneumotachograph. Ten minutes after induction of anaesthesia (50 mg/kg ketamine, 0.5 mg/kg diazepam) animals were intubated using a laryngoscope and a self-made tracheal tube (diameter inside: 1,5 mm, diameter outside: 2,0 mm) and connected to Validyne Pressure Transducer (Ponemah) aligned with a Carrier Signal Conditioner 13-7715-35 (CSC). The Ponemah Physiology Platform Model P3 Plus, Version 4.10-SP1 and software module Pulmonary airflow: PNM-PAF100W were used for analysis. Airflow was monitored continuously based upon differential pressure measurements. Once a regular breathing pattern after intubation was seen, breath per minute (BPM) and tidal volume VT (ml/breath) data were accepted for further analysis. Five minute interval analysis revealed an average of 50 BPM (SD: ± 20) and a mean tidal volume (VT) of 0.09 mL (SD: ± 0.057). In a former study manual counting in non-sedated animals revealed 96 to 101 BPM (own data). In unrestrained animals, 36-44 BPM were registered by telemetry (2). In summary, this investigation demonstrated the feasibility of respiratory rate and tidal volume measurements in sedated, intubated marmosets. (1) Mansfield (2003) Marmoset models commonly used in biomedical research. Comp Med 53, 383-392 (2) Horii (2002) Development of telemetry system in the common marmoset—cardiovascular effects of astemizole and nicardipine. J Toxicol Sci 27, 123-130

2297 PULMONARY DELIVERY OF MEASLES VACCINE: NON-HUMAN PRIMATE SAFETY STUDY.

R. Forster[1], T. Appelqvist[1], D. Brown[2], B. Cohen[2], G. Chalonner-Larsson[3], R. de Swart[4] and A. Henao Restrepo[5]. *[1]CIT, Evreux, France, [2]Health Protection Agency, London, United Kingdom, [3]Bioconsult, Ottawa, ON, Canada, [4]Erasmus University, Rotterdam, Netherlands and [5]WHO, Geneva, Switzerland.*

The pulmonary delivery of measles vaccine is of great interest for vaccination programs in developing countries, since it would bring benefits in terms of needle-free delivery and economical approaches to vaccination campaigns. Measles results in significant child mortality in developing countries every year. Since the pulmonary route is the natural route of infection by measles, pulmonary delivery is expected to be an effective route of immunisation. In the study reported here, we have evaluated the safety of pulmonary delivery of Edmonston Zagreb measles vaccine in cynomolgus monkey, a non-human primate which is susceptible to infection with measles. Vaccine preparations were administered to groups of monkeys on two occasions (Day 1 and Day 21) by nebuliser, at 5 fold the intended clinical dose (in terms of viral particles). Separate treatment groups received administrations with low droplet size (MMAD 1-5 µM), high droplet size (10 µM) measles vaccine, or placebo solution. In life clinical evaluations and laboratory investigations were performed and animals were sacrificed on Day 8 and Day 43 for terminal and post-mortem investigations. Administrations were well tolerated without evidence of local effects in the eyes, nose, mouth and throat. There was no mortality during the study. No effects were seen on body weight evolution, food consumption, ophthalmology, rectal temperature or clinical pathology. Water consumption was increased in measles vaccine treated animals with a corresponding increase in urine volume. Immunogenicity and viremia following treatment were characterised. A full range of tissues was evaluated for histopathological changes and no treatment-related findings were observed. It was concluded that pulmonary administration of Edmonston Zagreb measles vaccine was well tolerated locally and did not result in any evidence of systemic toxicity.

2298 LONG TERM CONTINUOUS INTRAVENOUS INFUSION IN THE ALBINO RAT, BEAGLE DOG, CYNOMOLGUS MONKEY AND GÖTTINGEN MINI-PIG.

A. Patel, L. Armer, M. Mus and C. Copeman. *Toxicology, Charles River Labs, Preclinical Services Montréal Inc., Senneville, QC, Canada.* Sponsor: C. Banks.

Continuous intravenous infusion via an indwelling catheter is frequently used in preclinical safety evaluation studies to mimic the proposed clinical route or to achieve higher blood drug levels. These studies have been conducted at our laboratory for over 20 years. Control data was evaluated to determine any effects of continuous intravenous infusion on the body weight gain, food intake/appetence and clinical pathology parameters over a 6 to 9 month period. A medical grade silicone-based catheter was surgically implanted under general anesthesia in the vena cava via a femoral vein. Animals were continuously infused with saline at rates of 0.4 mL/h (rodents) or 4 mL/h (non-rodents) for 24 hours/day, for 6 to 9 months, using a jacket and tether system. Body weight gains and food intake were unaffected when comparing data with historical control values for non-catheterized animals. Small differences in the clinical pathology data were observed between the catheterized and non-catheterized animals that could be associated with the presence of a foreign material.
It is concluded that in our laboratory the presence of an indwelling catheter and continuous intravenous infusion of saline at a rate of 0.4 mL/h in albino rats or 4 mL/h in beagle dogs, cynomolgus monkey or Göttingen mini-pigs for 6 to 9 months had no adverse effects on growth compared with non-catheterized animals. Clinical pathology changes were minor and consistent with the presence of a foreign material. The infection rate for the longer term studies also remained compa-