ON-LINE QUALITY CONTROL OF CYTOOTOXIC DRUGS: ULTRA-FAST CHROMATOGRAPHIC SEPARATION OF VINCA ALKALOIDS

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Background Due to repetitive and tedious handling tasks, production of anticancer drugs for infusion is associated with a high risk of non-conformity. Thus, on-line quality control is necessary to improve the quality of preparation. Since the quantities produced are ever growing, very fast analytical methods of control are needed to minimise the delay before release.

Purpose A high-performance liquid chromatography method has been developed for quality control of vinca alkaloid infusion bags (vindeine, vincristine, vinorelbine and vinblastine).

Materials and Methods The separation was optimised by a Doehlert experimental design using a mixture of those 4 alkaloids. Chromatography was performed using Prostar Varian chromatographic equipment with a Photodiode array Detector. A short Polaris C18 column (3 μm, 50 mm × 4.6 mm) was used for all separations. The optimization varied 3 parameters: pH of the phosphate buffer 25 mM (7.0–7.6), flow rate of the mobile phase (0.7–1.3 mL.min⁻¹) and proportion of acetonitrile (47–53%). 36 trials were necessary. The target response was the shortest run time giving a minimal resolution score of 1.5 for the most critical pair of peaks.

Results For vinorelbine, pH had a major effect on resolution. Optimal resolutions were obtained with a pH of 7.25. Then, the flow rate was set at 1.6 mL.min⁻¹ with a mobile phase consisting of water-acetonitrile (47–53 v/v). Under these conditions, resolution (47–53%) of vincristine, vinblastine and vinorelbine respectively. Methods were validated according to ICH criteria and are now routinely used without troubleshooting.

Conclusions This method allows in-line quality control of 4 vinca alkaloids in a very short time (less than 2 minutes) and constitutes a suitable and safe tool for chemotherapy preparation.

No conflict of interest.

PARENTERAL NUTRITION-ASSOCIATED CHELASTIS

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Background Parenteral nutrition-associated cholestasis (PNAC) results in significant morbidity and mortality. Progression to end-stage liver disease and subsequent hepatic failure is the most feared complication. A number of approaches have been proposed for the prevention and treatment of PNAC with mixed results.

Purpose To investigate the alteration of liver blood tests and the parenteral nutrition (PN) characteristics that trigger PNAC.

Materials and Methods Clinical blood tests and PN data of adults on artificial nutrition from January to August 2012 were collected.

Survival studies were conducted for each liver parameter studied. Primary endpoint was to fall above the upper limit of normal, considering them for women and men respectively: aspartate transaminase (AST): 32, 40 IU/L; Alanine transaminase (ALT): 78, 78 IU/L; gamma-glutamyl transferase (GGT): 55, 85 IU/L; alkaline phosphatase (ALP): 136, 129 IU/L; bilirubin: <1, <1 mg/dl.

PASW Statistics 19.0 and Microsoft Office 2007 were used.

Results One thousand eight hundred and ten PN bags for 124 patients (55% men) with mean 61 years old (18–95) were analysed.

Percentage of patients with values within limits after follow-up: bilirubin 92%; ALT 76%; ASP 59%; ALP 54%; GGT 27%.

Time until values went out of normal limits (days): ALT (13); ALP (13); ASP (12); bilirubin (12); GGT (6).

Age, gender, liver enzymes value before PN, and PN characteristics (volume, timing of infusions, calories, nitrogen and carbohydrates) were not significant PNAC trigger factors when considered individually.

Risk factor: initial value of bilirubin (each 0.1 mg/dL before PN, multiplies the risk of hyperbilirubinaemia by 14.5 times).

Protective factor: PN fat content (each gramme reduces the risk of high serum GGT concentration by 3.6%).

Conclusions The results show that PN poses a risk factor for PNAC, GGT being the test most affected.

However, none of the factors surrounding the PN and the patient, individually, account for the majority of the liver damage. On the contrary it is a conglomerate of different factors contributing to the final impairment. The lack of enteral nutrition also predisposes to PNAC.

This makes it difficult to find the right approach when prescribing PN. The indications for PN should be considered responsibly as should a return to enteral feeding whenever possible.

No conflict of interest.