Intensive Care Med (1995) 21:863–864

CORRESPONDENCE

M. G. Dehne
U. F. Kroh

Imipenem/cilastin dosage during acute renal failure and hemofiltration

Received: 9 August 1993
Accepted: 4 April 1995

Building on data published by MC Vos and colleagues in 1992 on imipenem/cilastatin and CAVHD [1] we investigated imipenem/cilastatin in 16 patients with ($n = 10$, group 1) and without ($n = 6$, group 2) renal insufficiency; both groups received continuous, volume-constant hemofiltration (CVHF). The indications for hemofiltration were oliguric renal dysfunction and increases in urea and creatinine of 8 mmol/day and 50 µmol/day, respectively. CVHF was performed as a postdilution technique with a polysulfone high-flux filter and an blood pump. The blood flow ranged from 100 to 200 ml/min and was adjusted to $Q_F = 20-30$ ml/min. The filter was discharged when transmembrane pressure reached 200 mmHg of when the volumes of filtrate dropped to 50% of the initial filtration rate. Anticoagulation was maintained with up to 1000 IU heparin/h to keep PTT at about 40 s. Arterial blood and ultrafiltrate samples were collected 10, 20 and 30 min and every hour from 1 to 12 h after the beginning of imipenem/cilastatin infusion. Pharmacokinetics were calculated under the condition of steady-state application. Curve approximation according to serum and cumulative ultrafiltrate levels was calculated by a least-square iteration process with the TOPFIT pharmacokinetic program.
A predictive algorithm for drug dosage during HF was developed to obtain a sufficient dosage without measuring blood levels. It was based on Dettli's equation for renal insufficiency [2]: $D = D_n (Q_x + Q_F \times S/Cl_n)$, where Q_x = individual extracorporeal elimination fraction; Q_F = filtration flow (ml/min); S = drug sieving (= 1-protein binding), and Cl_n of imipenem was taken from our control group. For imipenem, we presume only a low influence of Q_x on dosage because the normal Q_x ($= Q_O$) was 0.3.

Continuous, volume-constant hemofiltration is becoming recognized as the best treatment for ARF. This method replaced arteriovenous hemofiltration and dialysis because of its fewer side effects: CAVH depends on a sufficient blood pressure for Q_F, and dialysis sometimes affects patients' circulation.

Peak levels of imipenem were lower than those reported in the literature [3, 4]. Imipenem has a marked metabolic degradation, and therefore half-lives were only doubled compared to normals (group 1: 2.21 ± 0.59 h, group 2: 1.38 ± 0.41 h, normals: 1.0 h. This is the reason for the low calculated initial concentration and the lower area under the curve (AUC). The extrapolated initial concentration C_O has a mean of 30.7 mg/l, which, however, is still comparable to results of other authors [1, 3]. Sieving coefficient was calculated from the area under the curve of serum and ultrafiltrate because this method resulted in smaller standard deviations with respect to predictive values than from single data. Q_x of group 1 was always greater than the normal elimination. The dosage reduction factor was 0.4. Dosage corrections following CVHF are small compared to non-renal elimination. This would imply that the CVHF correction is comparable to untreated end-stage renal disease. Cilastatin has no antibiotic effect and accumulates during renal dysfunction. In patients with no kidney function, cislatin is not indicated. The results confirmed the prediction for ARF patients: the dose of imipenem/cilastatin has to be reduced from 4 g/day to 1.5–3.0 g/day in patients with ARF during CVHF.

References

1. Vos MC, Vincent HH, Yzerman EP (1992) Clearance of imipenem/cilastatin in acute renal failure patients treated by continuous hemodiafiltration (CAVHD). Intensive Care Med 18:282
2. Dettli L (1983) Arzneimitteldosierung bei Nieren- und Leberinsuffizienz. Therapiewoche 33:407
3. Drusano GL (1986) On overview of the pharmacology of imipenem /cilastatin. J Antimicrob Chemoth 18:79
4. Keller E, Fecht H, Böhler J, Schollmeyer P (1989) Single-dose kinetics of imipenem/cilastatin during continuous arteriovenous hemofiltration in intensive care patients. Nephrol Dial Transplant 4:640

M. G. Dehne (✉)
Department of Anaesthesiology and Intensive Care Medicine,
Justus-Liebig University,
Rudolf-Buchheim-Straße 7,
D-35385 Gießen, Germany

B. F. Fikkers
D. F. Zandstra

Primary laryngospasm in a patient with Parkinson's disease: treatment with CPAP via minitracheostomy following intubation

Received: 4 December 1994
Accepted: 4 April 1995

Sir: We would like to report on a primary laryngospasm in a patient with Parkinson's disease and its treatment with CPAP (continuous positive airway pressure) via minitracheostomy.

A 60-year-old man with about a 10-year history of Parkinson's disease treated with Sinemet (carbidopa and levodopa) was admitted to the hospital with a life-threatening upper airway obstruction. He was intubated, and mechanical ventilation was initiated. Chest X-ray revealed bilateral basal consolidations. After 3 days, the condition had improved, blood gases were normal and the patient could be extubated. Stridor immediately resumed, however. On fiberoptic bronchoscopy, the vocal cords appeared to be almost completely adducted without edema or signs of inflammation.
A minitracheostomy was performed and treatment with continuous-flow CPAP connected to the minitracheostomy was started. This resulted in a marked reduction of the stridor, with adequate ventilation. The patient was successfully weaned from this CPAP arrangement without recurrent laryngospasms and was transferred to the ward after 5 days with minitracheostomy in situ. Additional investigation with body-plethysmography breathing showed a marked increase in inspiratory resistance, with almost normal expiratory resistance, pattern in accordance with extrathoracic, variable airflow obstruction, e.g. vocal cord dysfunction. Episodes of severe stridor recurred after 2 weeks. On direct laryncoscopy, the vocal cords were still adducted. A permanent tracheostomy was performed to avoid further ICU admission and interventions.

In Parkinson's disease, dopamine depletion leads to diminished inhibition of the extrapyramidal motor system. This may lead to severe laryngospasm. Respiratory problems are well known, and aspiration pneumonia is one of the most common causes of death among such patients [1].

Dysfunction of the upper airways has only recently been recognized in patients with Parkinson's disease [2]. In most cases, this leads to impairment of static and dynamic pulmonary function. In some patients, laryngeal involvement was the main reason for airway obstruction [2]. In our patient, the most likely diagnosis is primary laryngospasm associated with Parkinson's disease.

Treatment by minitracheostomy connected to a continous flow CPAP resulted in a clinically relevant relief of stridor.

The mechanism of this effect might be the slight positive airway pressure of 2–4 cmH_2O in combination with a 4-mm free artificial airway. However, the latter cannot be the only explanation for the clinical relief of stridor, since the stridor increased while the patient was breathing through an open minitracheostomy without CPAP connection. Although minitracheostomy is most frequently used in the treatment of sputum retention, it allows an artifical airway to be combined with several other arrangements [3, 4].

In conclusion, laryngospasm caused by dysfunction of recurrent laryngeal nerves may be associated with Parkinson's disease. CPAP via minitracheostomy proved to be temporarily successful in the management of this problem. Tracheostomy may be inevitable in case of persistent relapses.

References

1. Vincken WG, Gauther SG, Dollfuss RE, Hanson RE, Darauay CM, Cosio MG (1984) Involvement of upper airway muscles in extrapyramidal disorders. N Engl J Med 311:438–442
2. Izquierdo-Alonso JL, Jimenez-Jimenez FJ, Cabrera-Valdivia F, Mansilla-Lesmes M (1994) Airway dysfunction in patients with Parkinson's disease. Lung 172:47–55
3. Squires SJ, Frampton MC (1986) The use of minitracheostomy and high-frequency jet ventilation in the management of airway obstruction. J Laryngol Otol 100:1199
4. Iapichino F, Gavazzeni, Mascheroni D, Bordone G, Solca M (1991) Combined use of mask CPAP and minitracheostomy as an alternative to endotracheal intubation. Intensive Care Med 17:47–49

B.F. Fikkers · D.F. Zandstra (✉)
Intensive Care Unit,
Onze Lieve Vrouwe Gasthuis,
1e Oosterparkstraat 279,
P.O. Box 95500,
NL-1090 HA Amsterdam,
The Netherlands

B. Levy
P.E. Bollaert
A. Larcan

Inhaled nitric oxide is often efficient in severe ARDS

Received: 29 November 1994
Accepted: 23 March 1995

Sir: In a recent issue of Intensive Care Medicine, Mira et al. [1] presented a study concerning the lack of efficiency of inhaled nitric oxide in ARDS. They reported a series of six patients with severe ARDS who did not respond to NO, three of whom responded to a subsequent trial of NO. It was suggested that soluble guanylate cyclase of pulmonary vasculature smooth muscle could be unresponsive to NO.

We used inhaled NO in 30 patients with severe ARDS ($PaO_2/FiO_2 = 81 \pm 8$ on FiO_2 1 PEEP 11±1; LIS = 3.45) [2]. NO (5 ppm) was administered early (mechanical ventilation for 7±2 days). Twenty-eight patients were considered to be NO responders (+20% PaO_2/FiO_2). We did not find any correlation between the improvement in arterial oxygenation and the decrease in mean pulmonary arterial pressure [PAPm = 29±3 at TO and PAPm = 28±2 at T1 hour (NS)]. The 2 NO non-responders had acute hemorragic pulmonary edema with refractory septic shock (SAP under 70 mmHg with high doses of epinephrine and norepinephrine). Owing to hemodynamic instability, PEEP levels were low and did not allow for alveolar recruitment. In such a situation, it is not surprising that an inhaled agent might be ineffecient.

According to published studies, 30–50% of patients are considered to be responders to inhaled NO [3, 4]. In ARDS, pulmonary hypertension is secondary not only to hypoxic pulmonary vasoconstriction, but also to increased Va/Q abnormality, atelectasis, loss of vascular bed and small vessel obstruction. Given this heterogeneous vascular insult, it does not seem surprising that pulmonary artery pressure was not dramatically changed. Several additional factors may interfere with the efficacy of NO in patients with severe ARDS: reduction or loss of the hypoxic pulmonary vasoconstriction (pulmonary infection, lung trauma, lung hyperinflation) and replacement of actively constricted small pulmonary vessels by fibrotic and irreversibly narrowed pulmonary vessels [5]. The last explanation may be of value for the patients presented by Mira et al. Indeed, as a reference center for LFPPV-$ECCO_2R$, they may have recruited a higher proportion of end-stage ARDS than we did. Modifications of pulmonary vasculature in late ARDS associated with large areas of non-ventilated, non-recruitable parenchyma may be responsible for a decreased response to inhaled NO.

Finally, the wide variation in responders to NO inhalation could be related to the patient' pulmonary vascular levels of guanylate cyclase, and also to the degree of pulmonary parenchyma and vascular fibrosis.

References

1. Mira JP, Monchi M, Brunet F, Fierobe L, Dhainaut, JF, Dinh-Xuan AT (1994) Lack of efficiency of inhaled nitric oxide in ARDS. Intensive Care Med 7:532
2. Levy B, Bollaert PE, Bauer P, Nace L, Audibert G, Larcan A (1995) Therapeutic optimization including inhaled nitric oxide in adult respiratory distress syndrome in a polyvalent intensive care unit. J Trauma 38:370–374
3. Wysocki M, Delclaux C, Roupie E, Langeron O, Liu N, Herman B, Lemaire F, Brochard L (1994) Additive effects on gas exchange of inhaled nitric oxide and intravenous almitrine bismesylate in the adult respiratory distress syndrome. Intensive Care Med 20:254–259
4. Lowson SM, McArdle P, Rich GF (1994) Variable responses to inhaled nitric oxide in patients with ARDS (abstract). Anesthesiology 81:A124
5. Marshall BE, Hanson CW, Frasch F, Marshall C (1994) Role of hypoxic pulmonary vasoconstriction in pulmonary gas exchange and blood flow distribution. Intensive Care Med 20:379–389

B. Levy (✉) · P.E. Bollaert · A. Larcan
Service de Réanimation Polyvalente
Hôpital Central,
F-59035 Nancy Cedex,
France