EFFECTIVENESS OF DIABETIC KETOACIDOSIS TREATMENT WITH LOW-DOSIS VENOUS INSULIN INFUSIONS

L. Koeva, D. Koev, A. Protopopova, R. Alahverdyan;
V. Nikolova, R. Yankova, T. Kyoseva, K. Hristozov

Key-words: diabetic ketoacidosis – insulin – hypercoagulation – lipids – renin-angiotensin-aldosterone system

Diabetic ketoacidosis (DKA) is one of the most frequent urgent and critical states in endocrinology. It results from diabetes mellitus decompensation provoked by various factors; notwithstanding the improved general medical care and, especially, the care for diabetes mellitus patients DKA incidence rate remains relatively constant during the recent decades. Nowadays epidemiological investigations indicate that there are 43 cases to 10 000 diabetic mellitus patients. Mortality rate varies between 1 and 19 per cent in different countries (7).

General principles of DKA treatment are determined by the character of disturbances occurred. They include as follows: normalization of metabolic disorders (mainly of carbohydrate one) by means of insulin therapy and restoration of glucose (glycogen) reserves in the organism; correction of water-electrolyte deficiency; elimination of acid-base disbalance; symptomatic treatment of functional disorders of different organs and systems accompanying (or preceding or having caused) diabetic coma.

Until recently, maximally rapid elimination of all disturbances was considered a basic principle of behaviour. That was why during the first hour of DKA an intensive insulin treatment at dosis of 80–300 U of rapidly acting insulin was carried out. However, the long experience in the last decade caused essential changes in the tactics of DKA treatment. The new principles of DKA treatment are realized mainly by means of administration of low insulin doses. In 1973, Alberti et al. (5) first introduced this method of DKA treatment. Recent investigations corrected many of the traditional concepts about DKA pathogenesis and the mechanism of insulin influence in this case. It was demonstrated that in numerous DKA cases and as a rule in the cases of hyperosmolar coma a high sensitivity to insulin was presented (6, 8).

Material and Methods

Since 1975, we introduced DKA treatment by using crystal insulin infusions at low doses according to an unified therapeutic schedule in the Clinic of Endocrinology of the Higher Institute of Medicine, Varna: venous dropwise crystal insulin "Pharmachim" infusion diluted in saline (3, 4). Crystal insulin amount was 8 U /500 ml/ hour during the first 6 hours each and then 20 U / 500 ml / 3 hours each. No human albumin was applied. Since the third hour of treatment, potassium preparations (potassium chloride or panangin) were intravenously administered and the amount of potassium introduced was in conformity with kaliemia established. Mean potassium level administered was 15–20 mMol/l. If, however, during DKA treatment hypokaliemia occurred and blood potassium level reduced below 3.5 mMol/l then injection speed of 2 per cent potassium chloride solution should be increased up to 40–50 mMol/hour (100 ml/hour).

Rehydratation was performed by physiological saline when blood glucose level was over 12 mMol/l (250 mg%) and by glucose serum when this level was below 13 mMol/l (250 m%).

Drug treatment of acidosis was administered at pH below 7.2:50 mMol (150 ml of 2.74 per cent sodium bicarbonate solution) were intravenously injected for 30 min. When pH was below 7.0, a total of 125 mMol (375 ml of this solution) were injected (3).

Results and Discussion

A total of 1340 DKA patients were treated after this method during a 10-year period. This number presented 42 per cent of all diabetes mellitus patients hospitalized in the Clinic. There were 547 males and 793 females. The way of treatment prior to DKA appearance was as followed: insulin therapy – in 828 patients, peroral one – in 440 while diet failute was in 32 patients and 40 cases were of newly-diagnosed diabetes mellitus. After treatment by our method blood glucose level reduced relatively rapidlier in the first 3 hours and then decreased gradually reaching its minimum of about 10 mMol/l on the 6th–8th hour (fig. 1). This slow and gradual

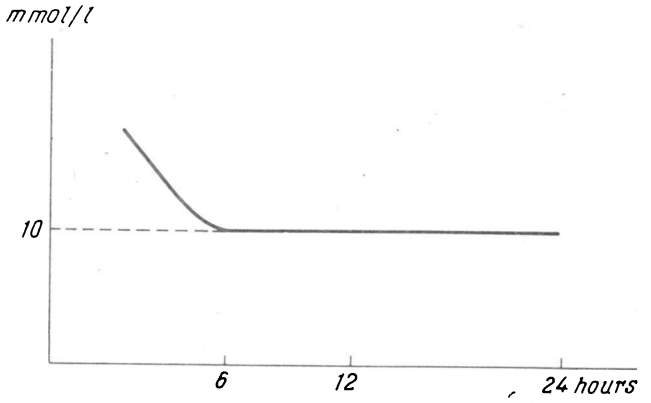

Fig. 1. Glycemia dynamics during treatment.

glucose level reduction is favourable for the patients because it excludes the risk of hypoglycemia and decreases the danger of sharp changes in the water-electrolyte balance. We do not use human albumin. This does not alter the effectiveness of the treatment but it reduces considerably therapeutic costs. In 1976, i.e. one year after introduction of this method by us, Peterson et al. (cited after 1) confute previous apprehensions that 1/4 of intravenously injected insulin retains on the wall of the bank and system tubules for infusions. These authors indicate that during infusion of the initial 50 ml of the fluid containing less than 0.1 U/ml insulin a complete saturation of absorption surfaces of the system sets in thus a further insulin loss is interrupted.

DKA was overcome in all the patients without any exception after the treatment carried out according to our schedule: disappearance of ketobodies in urine and blood sugar level reduction. However, the later results depended on the main disease inducing DKA (fig. 2). Of our patients, 1121 could compensate the diabetes mellitus and 119 ones died. The cardinal causes for lethal outcome were as followed: brain oedema in patients with severe cerebral circulation disorders and with severe water-electrolyte ones; acute cardiovascular accidents on the background of manifested ischemic heart disease; infectious-septic diseases; advanced chronic renal failure, etc.

Mean DKA duration was 8 hours. This period was shorter in patients with dietary errors and lapses in the treatment (at the average 6 hours) and most long-lasting in patients with bacterial

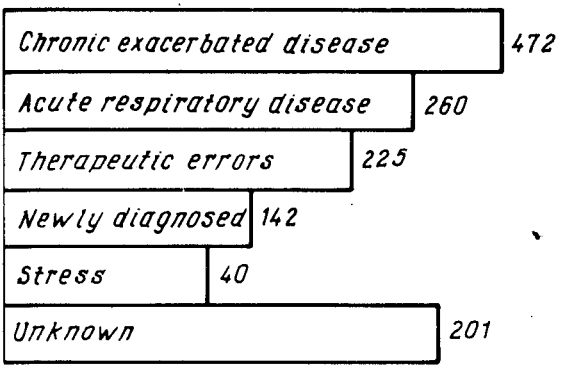

Fig. 2. Causes for DKA.

and viral infections (at the average 12 hours) while other cases occupied an intermediate position. Insulin dosage required to overcome DKA was presented on fig. 3.

We examined also some other biochemical parameters altered unfavourably by DKA. First they were coagulation changes. There was a tendency towards hypercoagulation due to haemo-

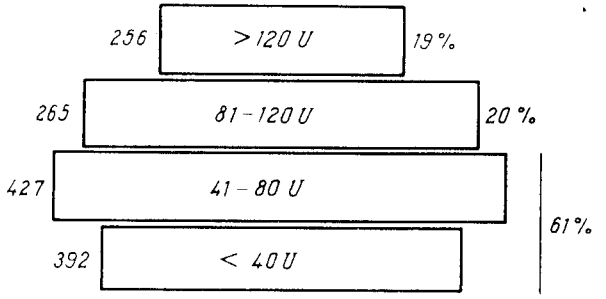

Fig. 3. Dosis of insulin.

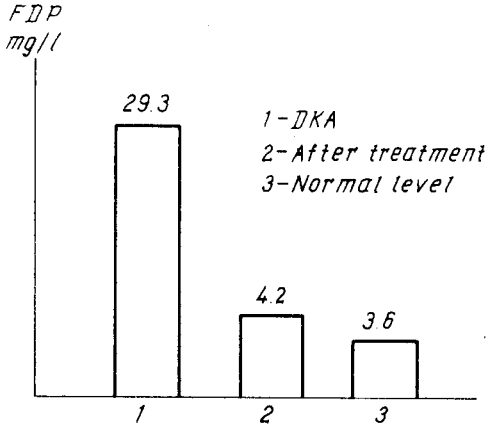

Fig. 4. Changes of fibrin-degradation products in DKA.

concentration in a case of ketoacidosis combined with metabolic and coagulation disturbances. These alterations were risk factors for intravascular coagulation and that was why we routinely used in our practice heparin in low doses when pH was below 7.2 (fig. 4). Low heparin doses were recommended as prophylaxis against thromboembolic complications (7). This therapy had insignificant side effects.

Lipid metabolism was also influenced favourably by our therapy. According to our data, ketoacidosis was characterized by lipid profile deviation in direction to prevalence of atherogenic lipoproteins and fatty acids. This therapy resulted in diminishing this trend and changing the lipid profile into an antiatherogenic direction (fig. 5).

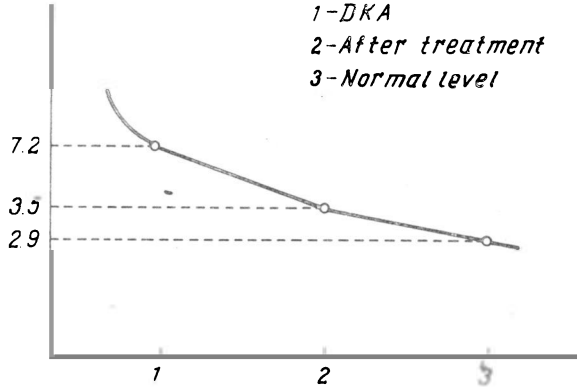

Fig. 5. Changes of atherogenic index in DKA.

Third some changes set in in the renin-angiotensin-aldosterone system which was strongly activated in DKA. Plasma renin activity and urine aldosterone excretion elevated repeatedly. Although these changes were compensatory concerning dehydratation they could influence unfavourably on the cardiovascular system functioning and worsen electrolyte disorders, especially hypokaliemia. After treatment renin activity normalized and acetonuria disappeared while increased urinary aldosterone reduced slowlier and remained over the normal level after acetonuria disappearance (fig. 6) (2). Our data suggested us to conclude that it was necesssary to rea-

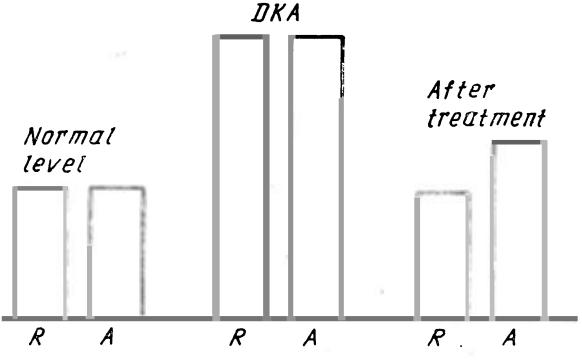

Fig. 6. Dynamics of renin-aldosterone secretion in DKA.

lize sodium and potassium monitoring and to perform a corresponding substitution therapy with potassium during the period after acetonuria disappearance, too.

The following conclusions can be drawn on the basis of our investigations:

1. At presence, DKA treatment with low-dosis crystal insulin is a method of choice. This method is very effective and results not only in acetonuria disappearance and hyperglycemia overcoming but also in elimination of other secondary metabolic disturbances.

2. Hypercoagulation due to haemoconcentration is a risk factor for intravascular coagulation in DKA cases and it is corrected by adequate therapy and administration of low heparin doses at pH below 7.2.

3. DKA treatment according to this schedule induces changes of lipid profile in an anti-atherogenic direction.

4. The strong activation of renin-angiotensin-aldosterone system in DKA requires sodium and potassium monitoring and substitution therapy by potassium preparations even after acetonuria disappearance.

5. The strongest efforts to reduce the danger of development of DKA should be directed to its prevention by means of education of both physicians and diabetes mellitus patients.

REFERENCES

1. Балабалкин, М. Н., В. С. Лукянчиков. Диабетна кома. – В: Клиника и лечение на критичните състояния в ендокринологията. София, Медицина и физкултура, 1985, 7–59. – 2. Коев, Д., и др. В: Ренин-ангиотензин-алдостеронова система. София, Медицина и физкултура, 1986, 170–194. – 3. Коева, Л., Д. Коев, В. Николова, В. Сиракова, П. Геров. *Вътр. болести*, 1978, № 3, 100–103. – 4. Попов, А., Л. Ваков, С. Златева, Д. Манолов. *Съвр. мед.*, 1977, № 1, 55–58. – 5. Alberti, F. W., A. Schofer. *Therapiewoche*, 28, 1978, No 50, 9754–9756. – 6. Alberti, K. G. M., D. Phil, M. R. Pathet al. *Med. Clin. North Amer.*, 62, 1978, No 4, 799–814. – 7. Kelier, V. *Diabetologia*, 29, 1986, No 2, 71–77. – 8. Menzel, R., E. Zander, E. Iutri. *Endokrinologie*, 67, 1976, No 2, 220–239.

ЭФФЕКТИВНОСТЬ ЛЕЧЕНИЯ ДИАБЕТИЧЕСКОГО КЕТОАЦИДОЗА ВЕНОЗНЫМИ ИНФУЗИЯМИ МАЛЫХ ДОЗ ИНСУЛИНА

Л. Коева, Д. Коев, А. Протопопова, Р. Аллахвердян, В. Николова, Р. Янкова, Т. Кесева, К. Христозов

РЕЗЮМЕ

Сообщаются результаты десятилетнего опыта клиники эндокринологии при Высшем медицинском институте в Варне, полученных при лечении диабетического кетоацидоза, примененном 1340 больным сахарным диабетом. Создана единая терапевтическая схема: венозная капельная инфузия малых доз кристаллического инсулина. Гликемия понижается медленно и постепенно, что исключает риск гипогликемии и уменьшает опастность в резких сдвигах водно-электролитного равновесия. Соответственно уровню калия применяются соответствующие коррекции хлоридом калия. Ацидоз подвергается влиянию бикарбоната натрия лишь в случае, что pH ниже 7.2. При тех же стоимостях pH применяются малые дозы гепарина с целью предупреждения тромбоэмболических осложнений. При диабетическом кетоацидозе сильно активируется ренин-ангиотензин-альдостероновая система. Это приводит к необходимости в замещающей терапии калием и в период после исчезновения ацетона в моче. Применяемая авторами лечебная схема для лечения диабетического кетоацедоза является внедрением чужого опыта с творческими модификациями, которые привели к определенному экономическу эффекту. Описанная схема внедрена в лечебную практиту всех больниц Северовосточной Болгарии.