DM

Letters

Discontinuing insulin therapy after diabetic ketoacidosis—is its cause worth considering?

We read with interest the paper by Hsin Yu *et al.* [1], and found it of significant practical importance. However, we believe that the authors missed an important issue in clinical characteristics of diabetic ketoacidosis (DKA), as no data on possible causes of DKA in the studied group are presented.

DKA might occur in diabetes at the onset of the disease, and later on due to insulin omission or infection [2,3]. It is less clear what causes DKA in newly diagnosed subjects, who later do not require insulin to control blood glucose. We suggest that a specific cause of DKA might also be a useful predictor of insulin discontinuation in further stages of the disease. We describe a case of a patient who was diagnosed with diabetes and DKA, in whom insulin was withdrawn after 2 months. He presented with all three factors associated with insulin discontinuation described by Hsin Yu *et al.* [1].

On 1 February 2001, the patient (male, Caucasian, aged 53 years, body mass index 28.7 kg/m^2) was referred to the Metabolic Diseases Department with DKA and an upper respiratory tract infection. His personal medical history was unremarkable, although three members of the patient's family were diabetic.

In the previous 3 days he had noticed increased thirst and polyuria. He presented with features of diabetic ketotic acidosis (blood glucose 41.1 mmol/l, pH 7.26, serum bicarbonate 9.8 mmol/l, base excess [–14.9] mmol/l), was dehydrated, tachypnoeic, and had symptoms of severe purulent pharyngitis. Other laboratory abnormalities included elevated leucocyte count (14 850/μl, with 83.7% of neutrophils) and significantly elevated creatinine kinase (CK) up to 50 880 IU/l (reference range 10–90 IU/l). Intravenous insulin as well as antibiotic and fluids were initiated and the patient's general condition improved promptly. CK levels decreased to normal values within 6 days as did his blood cell count. His initial daily insulin dose was 103 IU, after 7 days it decreased to 72 IU, and at discharge, after 15 days of hospital treatment, he was taking 52 IU of insulin per day in multiple doses. His anti-GAD assay was negative. Ophthalmologic and neurological examinations were unremarkable.

After hospital stay the patient's insulin requirement was decreasing steadily, and after 6 weeks insulin therapy was discontinued. He was switched to glibenclamide 5 mg t.i.d. Nevertheless, he experienced hypoglycaemia and eventually, after 4 months, all pharmacological treatment was stopped. His mean daily blood glucose was between 4.5 and 5.0 mmol/l and his diabetes was managed by diet.

The case is a good example of a person in whom insulin therapy discontinuation would be expected according to the criteria proposed by Hsin Yu *et al.* [1]. He was over 40 years of age at diagnosis, DKA was his first symptom of diabetes and he was overweight. However, we believe that the cause of DKA should also be taken into consideration. Severe infection is a well-known precipitating factor of ketoacidosis in diabetic patients [2]. Our patient developed DKA following severe pharyngitis, but within weeks of its treatment no longer needed insulin.

It would therefore be interesting to learn which subjects studied by Hsin Yu *et al.* presented with infection. This might be another factor predicting insulin discontinuation.

Finally, the general conclusion drawn from the work of Hsin Yu *et al.* and other observations [4,5] suggests that ceasing insulin therapy is not uncommon in diabetes patients. However, more studies are needed to shed light on this somewhat understudied area of insulin therapy.

L. Czupryniak, J. Ruxer, M. Saryusz-Wolska and J. Loba
Metabolic Diseases Department, Barlicki University Hospital No. 1, Medical University of Lodz, Lodz, Poland

References

1 Hsin Yu E, Guo H-R, Wu T-J. Factors associated with discontinuing insulin therapy after diabetic ketoacidosis in adult diabetic patients. *Diabet Med* 2001; **18**: 920–926.
2 American Diabetes Association. Hyperglycemia crises in patients with diabetes mellitus. *Diabetes Care* 2001; **24**: 1988–1996.
3 Czupryniak L, Drzewoski J. [Causes of hospital admission of diabetic patients aged ≥ 70]. *Medycyna Metaboliczna* 1999; **III**: 21–26.
4 Balasubramanyan A, Zern JW, Hyman DJ, Pavlik V. New profiles of diabetic ketoacidosis: Type 1 vs. Type 2 diabetes and the effect of ethnicity. *Arch Intern Med* 1999; **159**: 2317–2322.
5 Westphal SA. The occurrence of diabetic ketoacidosis in non-insulin-dependent diabetes and newly diagnosed diabetic adults. *Am J Med* 1996; **101**: 19–24.

No evidence for accumulation of insulin glargine (LANTUS)

The results of Heise *et al.* [1] in a recent issue of the journal are very valuable. They shed light on the question, whether the new long-term insulin glargine has any overlapping effects on the insulin concentration, if repeatedly injected. To my knowledge, these are the first published results of serum insulin levels where multiple injections have been investigated. Because almost all patients are repetitively injecting glargine, these profiles are much more important for clinical practice than those following a single dose.

However, regarding the presented curves, I doubt whether the conclusion of the authors that 'there is no accumulation of glargine' is correct in general.

At least two articles [2,3] have investigated the insulin levels after one single injection of glargine over 24 h and 30 h, respectively. The authors demonstrate that after the end of this investigation period there is still a significant level of free serum insulin present. It is unlikely that these levels will drop to zero immediately after these measurement periods. Therefore, this serum insulin would lead to a superposition with the next injection, if the dosing interval is 24 h, as has also been used in [1] and is usual with this long-term insulin analogue.

The assumption of elevated insulin levels in the case of repeated injections appears to be confirmed by the measurements of Heise *et al*. The curves in Figure 1a show a starting value of the free serum insulin level at the beginning of the day of about 200 pmol/l and a value of about 100 pmol/l at the end of the day. Because this differs significantly from the profile of one single injection, this difference must at first glance be attributed to the superposition of two injections. The authors have some reservations regarding possible disturbing effects of insulin lispro injections. As they were given shortly before the start of the experiment, they might contribute to the doubling of the insulin level in the morning.

If the insulin profiles are adjoined, a sawtooth-like curve would result. If my conclusions are correct, a superposition must be assumed, which is simply an accumulation of two adjacent injections, but stepwise accumulation within further days can not be observed.

An accumulation or superposition, that would reach its steady state as soon as the second day after starting glargine therapy, would have wide clinical implications, particularly if the insulin levels double: (i) the injection time must be considered more carefully; (ii) one should wait at least until the second day before the dose is increased; (iii) the dose adaptation, particularly the incremental dose from day to day, must consider the fact that the dose is partly superimposed on the insulin of the following day.

In conclusion, I do not doubt that a stepwise accumulation of insulin glargine over several days can be ruled out by these data. However, the more important question is: after how many hours or days is a steady state achieved with repetitive injections, and what is the difference in insulin levels of this steady state compared with a single injection? Achieving the steady state appears to happen on the second day, but the details are unclear. Because the clinical implications might be even more important than for the stepwise accumulation, this should be the subject of further investigations.

E. Biermann
Institut für Diabetesforschung, Krankenhaus München-Schwabing, Kölnerplatz 1, 80804 München, Germany

References

1 Heise T, Bott S, Rave K, Dressler A, Rosskamp R, Heinemann L. No evidence for accumulation of insulin glargine (LANTUS®): a multiple injection study in patients with Type 1 diabetes. *Diabetic Med* 2002; **19**: 490–495.
2 Heinemann L, Linkeschowa R, Rave K, Hompesch B, Sedlak M, Heise T. Time–action profile of the long acting insulin insulin-analog insulin glargin (HOE901) in comparison with those of NPH insulin and placebo. *Diabetes Care* 2000; **23**: 644–649.
3 Lepore M, Pampanelli S, Fanelli C, Porcellati F, Bartoicci L, di Vincenco A *et al*. Pharmacokinetics and pharmacodynamics of subcutaneous injection of long acting human insulin analog glargin, NPH insulin and ultralente and continuous subcutaneous infusion of lispro. *Diabetes* 2000; **49**: 2142–2148.

Reply

We thank the reader for his interest in our study. We do not fully agree, though, with his theoretical considerations that our results might show that insulin glargine accumulates over 2 days to an extent which has 'wide clinical implications'.

It was precisely the aim of our study to investigate—in view of the long duration of action of glargine shown in the previously mentioned glucose clamp studies [1,2]—whether or not insulin glargine injected over several days leads to a clinically meaningful increase in the metabolic effect and/or in free serum insulin levels. The results obtained indicate that insulin glargine does not accumulate to a clinically meaningful degree: we did not observe any changes in the mean doses of either glargine or lispro, neither in the run-in nor in the dosing period. Furthermore, the mean dose of insulin glargine did not change in the 7-day titration period, which is a clear indication that the effect of glargine did not accumulate to a clinically meaningful extent.

These results are confirmed by other investigations which were published recently. Fanelli *et al*. [3] did not observe a substantial increase in the metabolic effect of insulin glargine when injected over 7 days (AUC under the glucose infusion rates 17 ± 2.1 at day 1 compared with 19.8 ± 1.9 mg/dl per 32 h at day 7). Additionally, an investigation of the impact of different injection times of insulin glargine showed that the highest mean blood glucose concentrations always occurred just prior before the next injection of insulin glargine, regardless of whether it was injected before breakfast, dinner or at bedtime [4]. This clearly argues against a duration of a clinically relevant action of more than 24 h, and might even indicate that the duration of action of glargine might not be long enough for a once daily administration in some patients.

On the other hand, the reader is correct that the results of our study do not completely rule out a minor accumulation of insulin glargine, as there is indeed a minor rise in baseline free serum insulin concentrations compared with trough levels in our study. It should be kept in mind, though, that in our study insulin lispro concentrations were also high at baseline, so that they contributed to a major extent, if not completely, to this difference.

It is still under debate why the duration of action of insulin glargine was shown to be above 24 h in glucose clamp studies

whereas it seems to be considerably shorter in other studies. This might be, at least partly, due to the different doses applied in these studies (up to 0.4 U/kg in the glucose clamp studies [1] compared with a minimal dose of 0.18 U/kg in our study). It has not been investigated yet whether or not the duration of action of insulin glargine increases with rising doses, as has been shown for other short-acting and intermediate-acting insulin preparations [5,6].

In any case, we agree with the conclusion of the reader that the dose of insulin glargine should be kept constant for at least 2 days before any changes are made. This is a standard rule for many long- or intermediate-acting insulin preparations [7] which should also apply to insulin glargine, and which was part of the dose titration schedule in the phase 3 studies performed with insulin glargine. In addition, it might be worth looking into the impact of dose on the duration of action for insulin glargine to exclude a clinically meaningful accumulation of glargine also for higher insulin doses.

T. Heise on behalf of the authors
Profil Institut für Stoffwechselforschung GmbH, Neuss, Germany

References

1 Heinemann L, Linkeschova R, Rave K, Hompesch B, Sedlak M, Heise T. Time-action profile of the long-acting insulin analog insulin glargine (HOE901) in comparison with those of NPH insulin and placebo. *Diabetes Care* 2000; **23**: 644–649.
2 Lepore M, Pampanelli S, Fanelli C, Porcellati F, Bartocci L, Di Vincenzo A *et al.* Pharmacokinetics and pharmacodynamics of subcutaneous injection of long-acting human insulin analog glargine, NPH insulin, and ultralente human insulin and continuous subcutaneous infusion of insulin lispro. *Diabetes* 2000; **49**: 2142–2148.
3 Fanelli CG, Pampanelli S, Porcellati F, Rossetti P, Torlone E, Brunetti P *et al.* Pharmacodynamics of subcutaneous injection of insulin glargine after the first as compared to seventh day of its once daily administration in patients with T1DM (Abstract). *Diabetologia* 2002; **45**: A258.
4 Hamann A, Matthaei S, Rosak C, HOE901/4007 Study Group. Once-daily insulin glargine is effective and safe in patients with Type 1 diabetes regardless of whether injected before breakfast or dinner, or at bedtime (Abstract). *Diabetologia* 2002; **45**: A51–52.
5 Heinemann L, Woodworth J. Pharmacokinetics and metabolism of insulin lispro. Insulin Lispro: a New Rapid-Acting Insulin Analog, Chapter III. *Drugs of Today* 1998; **34** (Suppl. C): 23–36.
6 Heinemann L, Heise T, Ampudia J, Klepper A, Bender R, Starke AAR. Time action profiles of the intermediate-acting insulin analogue: des(64,65)-human proinsulin. *Diabetes Metab* 1995; **21**: 415–419.
7 Mühlhauser I, Spraul M, Berger M. Insulinsubstitutionstherapie inkl. Insulinpumpentherapie. In Berger M ed. *Diabetes Mellitus*, 2nd edn. München Jena: Urban & Fischer, 2000; 287–325.

Can hyperglycaemia cause jejuno-jejunal intussusception?

We read with interest the recent case report from McFarlane *et al.* reporting on an adult Afro-American patient with first manifestation of Type 2 diabetes and jejuno-jejunal intussusception. In an effort to explain the cause of intussusception in the described patient hyperglycaemia, diabetic ketoacidosis (DKA) and hyperkalaemia were included, and the authors state that abdominal pain and intussusception resolved with correction of blood glucose [1]. Only if all the known and organic causes of jejuno-jejunal intussusception are ruled out could a speculative conclusion be drawn that hyperglycaemia, ketoacidosis and hyperkalaemia caused intussusception.

In adults entero-enteric intussusception is uncommon but represents a distinctive clinical entity. It is generally led by an organic lesion that is usually a polypoid mucosal or submucosal mass or a Meckel's diverticulum [2]. Symptoms are often chronic (several weeks to several months) and patients may exhibit irregularly spaced episodic attacks of abdominal pain, nausea, distension and vomiting, due to cycles of spontaneous reduction and recurrence of intussusception. During an acute attack in some patients a non-tender abdominal mass may be palpable. For diagnosis the features of intussusception are considered pathognomonic in computed tomography (CT), but to include all causes of abdominal pain into differential diagnosis the performance of abdominal ultrasound may be useful, too [3]. However, intussusception in adults is rare and makes up only 1% of patients with bowel obstruction.

In general, many patients with DKA complain of abdominal pain. The presence of abdominal pain raises the important question of whether a primary intra-abdominal problem has precipitated decompensation, or whether the pain is a result of DKA. Recently, a strong association was observed between abdominal pain and metabolic acidosis [4].

Up to 90% of intussusception in adults is secondary to an underlying pathology, with approximately 65% due to benign or malignant neoplasm. Non-neoplastic processes constitute 25%, while idiopathic or primary intussusceptions account for about 10% [2]. A significant incidence of intussusception has been reported in patients with acquired immune deficiency syndrome, caused by a variety of infectious and neoplastic conditions of the bowel. Intussusception may follow and may be related to a variety of predisposing factors after abdominal surgery. Transient intussusception has been noted on CT in patients with coeliac disease, Crohn's disease and malabsorption, which was attributed to dysrhythmic contractions. There is a suspected correlation of duration of diabetes mellitus and gastrointestinal (GI) motility with changes of gastric emptying characteristics from delayed to accelerated [5]. Some correlation is described of acute hyperglycaemia and GI dysmotility, and weak correlation of hyperkalaemia or acidosis and GI motility [1].

Including all possible causes, it seems unlikely that hyperglycaemia, hyperkalaemia and acidosis caused intussusception in this patient. We suggest evaluation of all known possible causes of intussusception and additional performance of endoscopy [6]. Since the small intestine is relatively inaccessible to routine endoscopy for diagnosis of small intestinal pathology, an enteroclysis needs to be performed in this patient [7].

T. Lahousen, R. W. Lipp and W. J. Schnedl
Department of Internal Medicine, Karl-Franzens University, Graz, Austria

References

1 McFarlane SI, Byrne K, Shin J, Williams R. Intussusception in an adult patient with severe hyperglycemia—a case report. *Diabet Med* 2002; **19**: 611–614.
2 Gayer G, Zissin R, Apter S, Papa M, Hertz M. Pictorial review. Adult intussusception—a CT diagnosis. *Br J Radiol* 2002; **75**: 185–190.
3 Puylaert JBCM. Ultrasound of acute GI tract conditions. *Eur Radiol* 2001; **11**: 1867–1877.
4 Umpierrez G, Freire AX. Abdominal pain in patients with hyperglycemic crises. *J Crit Care* 2002; **17**: 63–67.
5 Lipp RW, Schnedl WJ, Hammer HF, Kotanko P, Leb G, Krejs GJ. Effects of postprandial walking on delayed gastric emptying and intragastric meal distribution in longstanding diabetics. *Am J Gastroenterol* 2000; **95**: 419–424.
6 Schnedl WJ, Reisinger EC, Lipp RW, Uggowitzer M, Mischinger HJ, Fickert P *et al.* Biliary obstruction due to duodenojejunal intussusception in Peutz–Jeghers syndrome. *J Clin Gastroenterol* 1996; **23**: 220–223.
7 Gill SS, Heuman DM, Mihas AA. Small intestinal neoplasms. *J Clin Gastroenterol* 2001; **33**: 267–282.

Reply

In our case report we have indicated that our patient had two abdominal computed tomography (CT) scans that did not show any evidence of organic lesion that could explain the intussusception [1]. Furthermore, we have been following the patient for more than 2 years so far, without evidence of malignancy, HIV disease, coeliac disease or malabsorption. There was also no recurrence of his abdominal symptoms and his stool occult blood test remained negative. This clinical presentation would lead to classification of intussusception in our patient as 'idiopathic', a condition that is well reported in the literature [2–5]. For example, in a large series of 236 patients with adult intussusception, diagnosed by abdominal CT scanning, 12% of the cases had no identifiable cause [5]. Some of these patients had been followed clinically for 20 months, similar to our patient, with no evidence of organic cause for the intussusception. However, in these 'idiopathic' cases there was no mention of the metabolic status of the patients at the time of intussusception.

Given the known association of hyperglycaemia and gastrointestinal (GI) dysmotility that was demonstrated in several studies of animals [6] and humans, both healthy [7,8] and diabetic subjects [9], we suggest that intussusception was related to hyperglycaemia in our patient.

Furthermore, we are aware of another case of proximal intussusception in a patient with diabetic ketoacidosis that resolved with metabolic correction (A. Delgado, personal communication). The case is being submitted for publication in a report that will cite ours as the first case report in the literature that suggested a link between hyperglycaemia, GI dysmotility and adult intussusception [1].

S. I. McFarlane[1,2], J. Shin[1,2], K. Byrne[3] and R. Williams[1,2]
Departments of Medicine, [1]Kings County Hospital Center and [2]Down-State Medical Center, Brooklyn, NY and Department of Emergency Medicine, [3]Jacobi Medical Center, Albert Einstein College of Medicine, Bronx, NY, USA

References

1 McFarlane SI, Byrne K, Shin J, Williams R. 'Intussusception in an adult patient with severe hyperglycaemia—a case report'. *Diabet Med* 2002; **19**: 611–614.
2 Barbiera F, Cusma S, Di Giacomo D, Finazzo M, Lo Casto A, Pardo S, *et al.* Adult intestinal intussusception: comparison between CT features and surgical findings. *Radiol Med (Torino)* 2001; **102**: 37–42.
3 Huang WS, Changchien CS, Lu SN. Adult intussusception: a 12-year experience, with emphasis on etiology and analysis of risk factors. *Changgeng Yi Xue Za Zhi* 2000; **23**: 284–290.
4 Gayer G, Apter S, Hofmann C, Nass C, Amitai M, Zissin R *et al.* Intussusception in adults: CT diagnosis. *Clin Radiol* 1998; **53**: 53–75.
5 Warshauer DM, Lee JK. Adult intussusception detected at CT or MR imaging: clinical-imaging correlation. *Radiology* 1999; **212**: 853–860.
6 Mostaghni K, Howard BR. The effect of changes in blood glucose on the motility of the duodenum in sheep. *Cornell Vet* 1976; **66**: 598–603.
7 Byrne MM, Pluntke K, Wank U, Schirra J, Arnold R, Goke B *et al.* Inhibitory effects of hyperglycaemia on fed jejunal motility: potential role of hyperinsulinaemia. *Eur J Clin Invest* 1998; **28**: 72–78.
8 Sims MA, Hasler WL, Chey WD, Kim MS, Owyang C. Hyperglycemia inhibits mechanoreceptor-mediated gastrocolonic responses and colonic peristaltic reflexes in healthy humans. *Gastroenterology* 1995; **108**: 350–359.
9 Feldman M, Schiller LR. Disorders of gastrointestinal motility associated with diabetes mellitus. *Ann Intern Med* 1983; **98**: 378–384.