RATIONAL TESTING

Investigating hirsutism

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This is a series of occasional articles outlining initial diagnostic approaches to clinical presentations.

When should we test for clinical hyperandrogenism and what are the best tests?

The patient

A 29 year old woman presented to her general practitioner because of facial hair that had worsened over the past three years. Her menarche had been at the age of 13 and her menstrual cycle was regular at 30 days. Her weight had been stable over the past two years, but she had previously put on 10 kg in weight over 18 months. She had an unremarkable medical history and was not taking any drugs. She had a body mass index of 34 and coarse terminal hair on her upper lip, chin, and stomach. No signs of virilisation (deepening of the voice, clitoromegaly, and loss of female body shape) were seen.

What is the next investigation?

Hirsutism is the presence of excess hair growth in women as a result of increased androgen production or increased skin sensitivity to androgens, or both. It should be distinguished from hypertrichosis, which is androgen independent and causes uniform growth of non-terminal (vellus) hair over the body, particularly in non-sexual areas; this condition can be familial, related to drugs (such as phenytoin or ciclosporin), or caused by non-endocrine disorders such as anorexia nervosa. The initial consultation should take into account ethnic differences (even mild hirsutism in Asian women may indicate excess androgen production),[1] any cultural norms, and the patient's expectations during assessment.

The most common causes of clinical hyperandrogenism are PCOS (72%), idiopathic (no other clinical or biochemical abnormalities) hyperandrogenism (23%), non-classic adrenal hyperplasia (4.3%), and androgen secreting tumours (0.2%).[2] For a diagnosis of PCOS—the most common cause of hirsutism—other causes of clinical or biochemical hyperandrogenism and menstrual disturbance (which was not present in this case) need to be excluded and the revised 2003 consensus criteria fulfilled (box 1).[3] The initial laboratory investigations include thyroid function tests and measurement of free androgen index, prolactin, 17-hydroxyprogesterone, and 24 hour urine cortisol (to rule out Cushing's syndrome if suspected). Pregnancy should be ruled out in women with "irregular" or absent menstrual cycles.

Sex hormone evaluations

Serum analysis fails to detect biochemical hyperandrogenism in about 20-40% of women with PCOS.[4] The table shows the diagnostic accuracy of these biochemical parameters. Measurement of total testosterone, even using modern immunoassays, has a low sensitivity for diagnosing PCOS.[5] High (for example, with the use of oral contraceptive pills) or low (for example, in insulin resistance[7] or obesity) concentrations of sex hormone binding globulin may affect total testosterone values. Measurement of sex hormone binding globulin enables calculation of the free androgen index (total testosterone concentration divided by sex hormone binding globulin concentration multiplied by 100).[8] In practice, total testosterone is often normal in PCOS but the free androgen index—a measure of bioavailable testosterone—is raised because sex hormone binding globulin is suppressed.

A high total testosterone concentration indicates that hyperandrogenaemia may be caused by an ovarian or adrenal tumour. Raised testosterone concentrations

Box 1 Revised 2003 criteria for diagnosing polycystic ovary syndrome (PCOS)[3]

Two of the following three criteria must be fulfilled for a diagnosis of PCOS:

- A clinical diagnosis of oligomenorrhoea or amenorrhoea—menstrual cycles longer than 35 days or fewer than 10 periods a year
- Clinical (hirsutism, acne, or androgen alopecia) or biochemical (raised free androgen index) evidence of hyperandrogenism
- Polycystic ovaries on ultrasound examination (box 2)

Late onset congenital adrenal hyperplasia, androgen secreting tumours, and Cushing's syndrome must be excluded in women with raised androgens; thyroid disorders and raised prolactin should be excluded in women with menstrual disturbances.

Box 2 Ultrasound imaging

Women with either menstrual irregularities or clinical or biochemical hyperandrogenaemia only should undergo pelvic ultrasound. Visualisation of the ovaries is better when the transvaginal route is used rather than the transabdominal route.

A polycystic ovary has at least one of the following:

- Twelve or more follicles in each ovary, each follicle measuring 2-9 mm in diameter
- Ovarian volume >10 ml

One polycystic ovary is sufficient for the diagnosis of polycystic ovary syndrome.

are seen in 60-80% of women with PCOS.[9] If the total testosterone is normal (<4.1 nmol/l) or only slightly raised (<5 nmol/l), then an androgen secreting tumour can be excluded. Testosterone concentrations more than 1.5-2 times the upper limit of normal or a history of rapid virilisation are likely to be associated with tumour associated hyperandrogenism. In such cases dehydroepiandrosterone sulphate and androstenedione should be measured to identify an adrenal or ovarian source of the hyperandrogenaemia.

Ultrasound imaging

Patients with either menstrual disturbances or clinical or biochemical evidence of hyperandrogenism alone should have transvaginal ultrasonographic imaging of the ovaries to look for polycystic ovaries (box 2). Because our patient had clinical hyperandrogenism only, to fulfil the 2003 revised diagnostic criteria for PCOS she will therefore need ovarian imaging.

Thyroid function and prolactin

Other diseases that could result in a similar clinical picture need to be excluded before the diagnosis of PCOS can be confirmed. Thyroid function should be measured because defective functioning can affect menstruation and hypothyroidism is associated with changes in hair, although this is usually a coarsening and dryness of the hair rather than true hirsutism. Prolactin should be measured because it affects the menstrual cycle, and it has been associated with hirsutism through an effect on the production of adrenal androgens. If prolactin concentrations are more than 1.5-2 times the upper limit of normal, other causes of hyperprolactinaemia—including the use of drugs, especially antipsychotic agents, and pituitary tumours—should be considered.

Serum 17-hydroxyprogesterone

Around 1-10% of women with hyperandrogenaemia will have non-classic congenital adrenal hyperplasia,[10] which is caused by partial 21-hydroxylase deficiency and is clinically indistinguishable from PCOS. The prevalence is higher in Hispanics, Yugoslavs, Eastern European Jews, and people from the southern Mediterranean. In patients belonging to these ethnic groups, 17-hydroxyprogesterone—a precursor of 21-hydroxyprogesterone—can be used to screen for this condition. Blood should be taken in the follicular phase (the first half of the menstrual cycle) around 9 am to avoid diurnal variation. Under these circumstances, a 17-hydroxyprogesterone value of 5 nmol/l has a sensitivity of 100% and specificity of 88.6% for diagnosing non-classic congenital adrenal hyperplasia.[11] If 17-hydroxyprogesterone concentrations are raised, referral to an endocrinologist is warranted—the diagnosis will be confirmed if the 17-hydroxyprogesterone concentrations are higher than 30 nmol/1 after an adrenocorticotrophin stimulation test.[12] Our patient did not belong to an ethnic group with a high prevalence of non-classic congenital adrenal hyperplasia.

Twenty four hour urinary cortisol

Cushing's disease is a rare cause of hirsutism and its routine exclusion is not warranted unless the patient has cushingoid features. Estimation of 24 hour urinary cortisol excretion is a useful screening test. Basal 24 hour urinary cortisol excretion of more than three times the upper limit of normal (50-250 nmol/24 h) has a sensitivity of 100% and specificity of 98% in the diagnosis of Cushing's syndrome.[13] Our patient had no clinical signs of Cushing's syndrome.

Diagnostic outcome

Our patient's symptoms of clinical hyperandrogenaemia (hirsutism) and a regular menstrual cycle were not sufficient for a diagnosis of PCOS (box 1). Laboratory tests showed biochemical hyperandrogenaemia—total testosterone was normal (2.4 nmol/l; normal 0.5-3.4), sex hormone binding globulin was low (24 mmol/l; 32-58), so the free androgen index was high (10; <9). Thyroid stimulating hormone and prolactin concentrations were normal. To confirm a diagnosis of PCOS, she underwent ultrasound examination, which demonstrated polycystic ovaries (box 2). Because PCOS is associated with an increased risk of other long term problems—such as type 2 diabetes mellitus, hypertension, and dyslipidaemia—these should be considered during the patient's long term care.

Biochemical parameter used to test for hyperandrogenism

Biochemical parameter	Cut-off value	Sensitivity (%)	Specificity (%)	Positive likelihood ratio	Negative likelihood ratio
Total testosterone[5]	2.37 nmol/l	72.7	74.2	2.81	0.37
Sex hormone binding globulin[6]	37 nmol/l	88	87	6.63	0.14
Free androgen index[6]	3.67	75	86	5.30	0.29

LEARNING POINTS

Clinical hirsutism is usually caused by polycystic ovary syndrome or is idiopathic (has no other clinical or biochemical abnormality)

Initial tests should: assess biochemical hyperandrogenaemia by measuring total testosterone, sex hormone binding globulin, and free androgen index; include thyroid function tests and prolactin measurements; and if clinically indicated, rule out non-classic congenital adrenal hyperplasia by measuring 17-hydroxyprogesterone and Cushing's syndrome by measuring 24 hour urinary cortisol

Ultrasonographic imaging of ovaries is not needed to diagnose polycystic ovary syndrome in patients with menstrual disturbances and clinical or biochemical evidence of hyperandrogenism

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PRACTICE POINTER

"I need a note, doctor": dealing with requests for medical reports about patients

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Most doctors will have experienced the sinking feeling that denotes an impending ethical dilemma when faced with a request for a medical report or certificate

Doctors are often asked for information about their patients by third parties (employers, government agencies, insurance companies, regulatory bodies, and many others). Any doctor may receive such requests, but in the United Kingdom they come most often to general practitioners (table 1) because general practices hold the most comprehensive patient records.

A form may need to be filled out, or the doctor needs to write a letter. The response may be a certificate, a statement, or a report; this makes no difference and I will call them all reports. Some are straightforward, but others pose difficulties: conflicts of interest between patients and third parties, uncertainty about the information the doctor possesses and how to present it, and problems about payment. Classifying them may help us understand the problems better.

Classes of medical report

Legal reports that advance patient care

Recommendations under the Mental Health Acts,[1] reports for child protection,[2] and assessments of mental capacity[3] are closely linked to normal treatment and are almost part of it. Ethically they resemble referrals and requests for investigation, except that legal procedures are involved and normal rules of consent do not apply.

The public good

All doctors have duties to the public. Notification of infectious diseases [4]and adverse drug reactions[5] are public health functions of personal doctors,[6] although they are not always carried out conscientiously.[7] Death certification provides epidemiological information and also partly serves public health but, like cremation certificates and reports to coroners, death certificates also serve the public good by detecting unlawful killing, deliberately or by

neglect (not always successfully, as the Shipman case showed). Court reports on criminal injuries also advance the public good, though they do not advance public health.

Consent is usually not required for these legal obligations, although it is good practice to tell patients that these reports are being made when possible. Such reports breach confidentiality but there is no conflict of interest, since patients do not suffer (and may benefit) from this reporting process.

Illness as entitlement or excusing factor

Certification of illness is the largest and most difficult category. Illness is an important excusing factor—from work; from duties like jury service, attendance at court, probation, or community punishments; for delay or poor performance in academic assessments; and for other activities.[8] The commonest, certification of incapacity to work, has generated a considerable literature and controversy.[9 10] Illness also entitles patients to benefits like sick pay and incapacity benefit, free prescriptions, and preferential access to social housing and parking.

The relation between entitlement and excusing resembles that between claim rights and liberty rights.[11] Entitlement is a claim on grounds of illness; excusing is a liberty on similar grounds. In either case there may be conflict of interest between patients, who want the benefit or exemption, and the third party, who pays for it. Doctors must be truthful, but are usually predisposed to advance their patient's interests.

Fitness for sports

Fitness for sports may concern dangerous sports such as parachuting and bungee-jumping, but reports are also requested for more mundane activities like gym training and marathon running. Criteria for requesting reports vary. The British Sub-Aqua Club has abandoned reports as valueless,[12] although organisers of less risky activities may ask for reports.

If someone who is not fit takes part in a sport then they are at risk, so when reports are given to the sport's organisers, who also wish to avoid risk, there is rarely a conflict of interest. But there may be conflict between patient and doctor if they disagree about whether a health problem is relevant.

Fitness for an occupation

Occupations needing reports include driving lorries (heavy goods vehicles) and vehicles carrying passengers (taxis, buses, etc) and health professions such as occupational therapy and physiotherapy. These are jobs in which those unfit to practise pose some physical or mental risk to the public. They are usually activities where individuals are licensed and work for different employers or themselves. For work that is only possible in large organisations, such as driving trains or flying commercial aeroplanes, occupational health services assess these risks and personal doctors are rarely involved.

Here the focus is the public good. Someone working while unfit may injure himself or herself and incur civil and even criminal penalties, but the purpose of reports is not primarily to prevent this. Higher standards of fitness are required for driving buses or lorries than cars because they are more lethal and the risk to the public is greater. The same applies to professional practice. Concern for patients rather than practitioners is the guiding principle of the Health Professions Council in identifying those whose illness may affect their practice.[13] Although the Driver and Vehicle Licensing Agency and taxi licensing authorities provide detailed guidance on relevant health factors, the Health Professions Council's guidance is vague; why is not clear.

Information for actuarial assessments

Actuarial assessments are usually called insurance or PMA (personal medical attendant) reports. They help insurers assess an individual's risk of disability or death more accurately and weight the premium accordingly.

A clear conflict of interest arises here.[14] Information indicating increased risk disadvantages the patient: cover may be denied or premiums raised, but insurers benefit from accurate actuarial predictions. Consequently there has been much negotiation and legislation about these reports. The framework governing them in the UK is clear.[15 16] Consent is written and explicit, although inevitably constrained, as agreeing to a report is a condition of obtaining the insurance; and since patients may not know what is in their records or understand the implications of its disclosure, consent is not necessarily fully informed. There is usually provision for independent medical assessment if the general practitioner cannot or will not provide a report, and patients can view the report and withhold any information that they do not want divulged.[16]

Table 1 | Medical reports in British general practice

Purpose	Examples
Legal proceedings to advance patient care	Child protection reports, recommendations under the Mental Health Act, mental capacity assessments
To advance the public good	Notification of infectious diseases, adverse drug reactions, death and cremation certificates, evidence of injuries for criminal proceedings
Illness as an excusing factor	Certificates relating to short and long term incapacity to work (Med3, Med 5, Med 4, IB113) Countersignature of claims for holiday insurance Letters and reports for academic mitigation Letters of support for absence from court Letters of support for exemption from jury service
Illness as grounds for entitlement	Exemptions from paying medical and maternity prescriptions (FP92A, FW8) Housing letters Social security letters Forms related to disabled parking badges Forms for disability and mobility allowance War pensions Holiday insurance cancellation or curtailment Accounts of medical events for civil proceedings
Fitness assessment to take part in "dangerous" sports	Parachuting Paragliding Bungee jumping Gym for perceived "high risk" groups Sports for the disabled
Fitness to engage in a particular occupation or profession	Health Professions Council PSV and HGV licences Taxi driver Camp America
Actuarial calculation	Life assurance Sickness insurance

Table 2 | Ethical issues in medical reports

Purpose	Consent	Benefit to patient	Who pays?	Possible conflict of interest
Legal proceedings to advance patient care	Not obtainable	Yes	State	No
To advance the public good	Not required	No	State	No
Illness as an excusing factor or as grounds for entitlement	Required but sometimes constrained or inadequately informed	Yes	Patient or third party	Yes
		Yes	Patient or third party	Yes
Fitness to take part in dangerous sports	Yes but sometimes constrained	Yes	Patient	No
Fitness to engage in a particular occupation or profession	Yes but constrained	Little	Patient	Yes
Actuarial calculation		No	Third party	Yes

Non-medical reports

For some reports doctors act as responsible citizens rather than professionally—for example, countersigning passport applications and confirming identity. These are not considered further here.

Ethical problems

Consent

Although reports breach confidentiality, either the patient requests the report, implying consent, or signed consent is given. Its validity is more problematic.[17] Reports are often a condition for obtaining some good (insurance, an activity holiday, incapacity benefit). Consent is free only insofar as the patient is free not to seek that good. When consent is given, patients rarely know what is in their medical record, and they cannot know how the doctor will present that information. This is why the right to see the report[15] is important, but legislation does not cover all reports.

Conflict of interest

Many problems stem from conflicts of interest between the patient and the third party. How these affect different types of report is summarised in table 2. When the evidence is clear and favours the patient there is usually no difficulty. But when information may harm patient's interests (even non-clinical interests) or there is room for doubt about the patient's case (and there often is) the personal doctor's role as patient advocate and the overriding responsibility to tell the truth may create an uncomfortable position. Adverse reports may damage doctor-patient relationships, and doctors may feel constrained to "spin" the data to improve a dubious case.

Payment

Payment does not always come from the beneficiary, although logically the doctor should act in the interests of whoever pays for the report. This is not always recognised by patients or third parties.

For many reports the fee and who pays is clear. Sometimes this is negotiated between the medical profession and the relevant authority.[16] Some reports are part of the general practitioner's NHS contract. But many reports are not covered by the NHS; rightly so when they are not government functions. Sometimes (as for medicals related to driving licences) there is an advertised fee and patients expect to pay.

Often things are not clear. For example, charitable organisations offering activities to seriously ill or disabled patients sometimes ask doctors to certify fitness. Social security and housing authorities request letters to support loans from the social fund or to confirm medical conditions related to housing need (often using the patient as a messenger). Students ask for evidence of extenuating circumstances for academic authorities. These often cause the doctor embarrassment. The report would not be required if the patient (who is used to medical services being free at the point of use) were not vulnerable or in need. Asking them to pay seems hardhearted; the third party expresses no willingness to bear the cost; but why should the cost of preparing the report fall on the doctor or the NHS?

There is not always a clear and agreed basis for determining fees. Reports take medical and administrative time and involve extra cost when a consultation is booked specifically to request a report. Should fees depend on the time taken to prepare the report or put a value on the information given? NHS records have been compiled at considerable cost, often by many individuals over years. It is not clear how this information can be valued, or to whom it belongs.

Information and how it is presented

Reports often ask for information that the doctor does not or cannot possess. General practice records may have gaps, through mislaid records when people move, mislaid hospital letters, complementary and private practitioners who do not send reports to general practices, NHS services like walk-in centres and clinics, etc.

Even if there are no gaps, general practice records do not always include the information needed. General practitioners don't routinely collect the information on functional capacity that some reports request, so it is no surprise that "GP records are useful in providing evidence of diagnosis or health conditions, but less useful for judging functionality."[18] This data might be better obtained from practitioners who focus on function (physiotherapists, occupational therapists), but the tradition of asking the doctor mostly remains.

Even when information is available, its validity may be questionable. Much information in medical records comes from patients' histories, not direct observation. Symptoms in the patient's inner life—pain, anxiety, depression, headache—can never be directly observed, although behavioural data may support their presence. Even symptoms that are, in principle, objectively verifiable are usually documented from the history. Doctors rarely observe diarrhoea or vomiting, but accept the patient's word. In court this would be inadmissible "hearsay" evidence, yet in reports is often used for quasi-judicial judgments.

What is relevant in a report depends on the context, but personal physicians do not always know this—nor do requests always make that clear. What is the work of an occupational therapist or a counsellor at a children's

summer camp, and what health problems might affect it? What conditions increase the risk of parachute jumping? Some requests ask clear, factual questions and give detailed guidance; others do not. Some ask for judgments against defined criteria and others leave it to the discretion and the professional judgment of the individual doctor"[13] to decide what is relevant.

Doctors prefer to be asked for facts, not judgments. Reporting facts can be seen as more objective and less likely to lead to conflict of interest than judgments for or against a patient. Simple facts may be more reliable than complex judgments. Where reports from many doctors are used to decide who qualifies for a benefit (for example, disabled parking) factual reports are more likely to be fair. They also avoid problems of competence which concern doctors asked for judgments outside their clinical experience. But an element of judgment occurs in selection and presentation of even the simplest data.

Conclusion

It is not clear why reports that ask for judgments from someone not well informed or competent to make them, or are based on secondhand evidence, are requested. Since much of the information comes from patients it might be better to ask them directly (as does the BSAC sport diver medical form, www.bsac.org/uploads/documents/memberservices/self_declaration_medical_form.pdf). Sometimes it seems that general practitioners are being used to check on the patient's truthfulness (for example, the question "According to these records and your knowledge of the applicant, do the answers given by him/her in the questionnaire appear correct?" appears in the British transport police medical history questionnaire (http://tinyurl.com/7rlqvx)), but this conflicts with their role as patient advocates. General practitioners sometimes suspect that organisations like to think they can transfer responsibility for risk to them (I Sutherland, personal communication), or there may be naive but genuine ignorance of the limits of doctors' competence and knowledge of their patients.

Questions to be considered when completing a report

Classification—What class does the report fall into?

Consent—Has the patient consented? Is the consent free and informed?

Advantages—To whose advantage is it that the report is given?

Alternatives—What are the alternatives to giving the report, and what are their consequences?

Validity—How valid is the information on which the report is based?

Expenses—Who will pay for the report, and is the fee appropriate?

Responsibility—What are you being asked to do: provide information or make judgments? Are you comfortable taking responsibility for doing what you are being asked to do?

There is no obligation to provide reports. If a doctor lacks information or feels unable to make a judgment then saying so may be best. Sometimes independent medical assessment is an alternative, but often patients are disadvantaged by systems that expect a report if their doctor refuses to provide one. Problems might be avoided if alternatives, such as self certification, independent medical advisers, or use of other health professionals with more appropriate expertise, were explicitly and routinely available.

Many reports are justified. Despite its limitations the general practice record provides information that would be expensive or difficult to collect in other ways. General practitioners are accessible, and although our competence is sometimes overestimated, what sensible reports require is often within our capacity. When the ethical issues have been thought through and appropriate procedures developed, reports can be useful and unproblematic—but difficulties arise for doctors, patients, and third parties if these issues are ignored. A list of questions to consider when you are asked for a report is given in the box.

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DRUG POINT

Topiramate can induce hypoadrenalism in patients taking oral corticosteroid replacement

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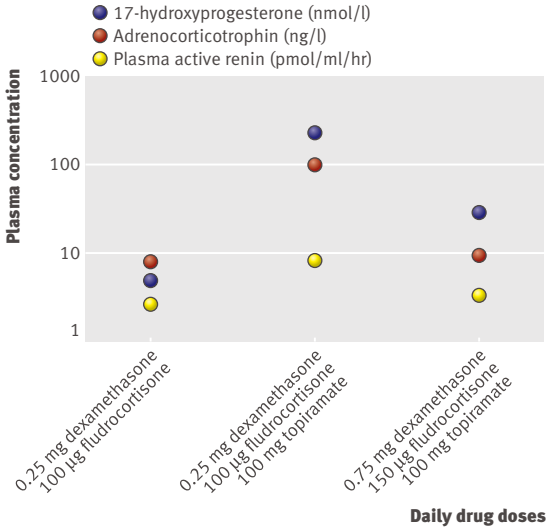
Case history

A 35 year old woman was taking life long glucocorticoid (dexamethasone) and mineralocorticoid (fludrocortisone, Florinef, Squibb) replacement for congenital adrenal hyperplasia caused by 21-hydroxylase deficiency. She started taking topiramate (Topamax, Janssen-Cilag) in March 2005, and the dose was titrated to 100 mg daily for atypical seizures secondary to mesial temporal sclerosis.

Before starting topiramate she had been taking stable doses of dexamethasone (0.25 mg a day) and fludrocortisone (100 µg a day), with biochemical evidence of good control of her congenital adrenal hyperplasia (figure). Within a few weeks of starting topiramate she complained of tiredness, nausea, weight loss, and muscle aches.

A diagnosis of hypoadrenalism was supported by raised plasma 17-hydroxyprogesterone, adrenocorticotrophin, and plasma renin activity. The rises in 17-hydroxyprogesterone and adrenocorticotrophin indicate an inadequate replacement dose of glucocorticoid (dexamethasone), and the rise in plasma renin activity indicates an inadequate replacement dose of mineralocorticoid (fludrocortisone).



Plasma concentrations of the cortisol precursor 17-hydroxyprogesterone, adrenocorticotrophin, and plasma renin activity, indicative of undertreatment of congenital adrenal hyperplasia. Increase in the daily doses to 0.75 mg dexamethasone and 150 µg fludrocortisone resulted in biochemical improvement

Discussion

Topiramate, an antiepileptic, is a dose dependent, weak inducer of the hepatic cytochrome CYP3A4, which is involved in steroid metabolism.[1,2] Evidence of accelerated clearance of oestradiol induced by topiramate has resulted in a "packet insert" caution about reduced effectiveness of the oral contraceptive pill.

In our patient a modest dose of topiramate accelerated the metabolic clearance of dexamethasone and fludrocortisone, manifest by a greater than fivefold increase in the concentrations of the cortisol precursor 17-hydroxyprogesterone, adrenocorticotrophin, and plasma renin activity, combined with symptoms of hypoadrenalism. The Medicines and Healthcare Products Regulatory Agency responded to our report by stating that no other glucocorticoid interactions had been reported to the agency or the Commission for Human Medicines.

The manufacturer acknowledged the theoretical possibility of a pharmacokinetic interaction between topiramate and corticosteroids but has no other reports. The ability of topiramate to accelerate glucocorticoid and mineralocorticoid clearance to induce hypoadrenalism is not confined to patients with congenital adrenal hyperplasia but is applicable to any patient who is taking a fixed dose of glucocorticoid replacement. Such patients should be warned of the risk of hypoadrenalism.

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LESSON OF THE WEEK

Diabetic ketoacidosis caused by exposure of insulin pump to heat and sunlight

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Patients with diabetes need to know how to store insulin

Use of continuous subcutaneous insulin infusion is increasing worldwide.[1] This method of insulin delivery was thought to have advantages in children, including better control of blood glucose, HbA_{1c}, and hypoglycaemic episodes, compared with multiple daily injections.[2-8] A recent meta-analysis, however, showed that the benefits might not be as great as was previously hoped, particularly in younger children.[9] In the UK, guidelines from the National Institute for Health and Clinical Excellence recommend continuous subcutaneous infusion when multiple dose therapy has failed in patients with HbA_{1c} concentrations greater than 7.5%.[10]

A disadvantage of using a pump is that ketoacidosis can occur quickly if a problem with insulin delivery occurs, because no background of long acting insulin is available. We describe a case of diabetic ketoacidosis caused by insulin degrading in the reservoir of a pump in sunlight and heat.

Case report

An 11 year old girl with type 1 diabetes presented to the emergency department with vomiting and abdominal pains. She had a blood glucose concentration of 20.6 mmol/l, ketonuria (+++), and acidosis (pH 7.14). She had had diabetes since age 7 years and had been using an insulin pump for 11 months. Control of her condition had been reasonable (HbA_{1c} 7.9%). At presentation, she was wearing her insulin pump (Medtronic 522); no signs of inflammation or lipohypertrophy were present at the insertion site, and the pump was delivering insulin at the programmed rate.

The patient was managed with intravenous insulin and fluids in accord with conventional guidelines for diabetic ketoacidosis, and improved quickly. Subcutaneous insulin (Humalog, Lilly) was restarted at her usual basal rate (0.8 units/h) via the pump the following morning (fasting fingerprick glucose 4.2 mmol/l, pH 7.35, blood ketones negative). Within an hour, her fingerprick glucose concentration had risen to 18.1 mmol/l. A corrective bolus of insulin was given using the pump, but her glucose concentrations continued to rise; measurements of 19.5 mmol/l and "Hi" were obtained 30 min apart. Insulin was then given by injection and the infusion set was changed; two hours later, the patient's glucose concentration fell to 8.3 mmol/l, but it rose again later in the day, after the pump was reconnected. At this point, the insulin in the pump's reservoir was changed; thereafter, the patient's glucose concentration returned to normal on her usual basal and bolus doses. The admission occurred at the weekend and the diabetes team was not involved in the management.

Two days before admission she had disconnected the pump for swimming—manufacturers recommend disconnection for up to an hour for such activities.[11] The pump had been left on a table by the side of a pool in direct sunlight on a hot Australian summer's day (35°C). Later in the day, after the pump had been reconnected, the patient's blood sugar began to rise and she had a trace of urinary ketones. A correction dose of insulin was given by needle and the infusion set was changed. Nevertheless, the patient's blood sugar levels remained high the next day, and she presented in diabetic ketoacidosis about 48 hours after the incident.

Discussion

We propose that by exposure to high temperatures through being left in direct sunlight, the insulin in the pump reservoir was destabilised and made ineffective. Our patient partly followed guidelines for hyperglycaemia by injecting a correction dose of insulin and changing the infusion set, but she did not change the insulin in the reservoir. The correction dose probably delayed her presentation to the emergency department.

All patients using pumps are taught to disconnect and replace the tubing and to replace the insulin in the reservoir if they suspect that insulin is not being delivered correctly. This process eradicates common causes of delivery failure, such as air bubbles in the infusion set, occlusion or leakage of the line, or omission of insulin. The patient is taught that if blood glucose concentrations do not fall rapidly with a correction bolus from the pump, they should give themselves an injection of insulin while working out the cause of the fault.

Recommendations for storage of insulin suggest the drug can be kept at room temperature for up to three or four weeks. Advice is available on manufacturers' websites. Eli Lilly state that cartridges should be kept in a fridge between 2-8°C, may be kept below 30°C for up to 28 days, and should not be placed near heat or in the sun. NovoNordisk's website says that after opening, insulin in vials is stable for up to 3 months in the

refrigerator and 6 weeks at 25°C, insulin in cartridges is stable for up to 4 weeks after opening if stored at 25°C, and brief exposure to extreme temperatures need not necessarily reduce its efficacy.[12]

High temperatures and exposure to light increase the degradation of insulin to transformation products (deaminated insulin, covalent dimers, and higher oligomers) and increase formation of fibrils, potentially causing a loss in biological potency.[13] Our patient was using Humalog, a form of insulin lispro. This form of insulin is stable for up to seven days under conditions simulating the pump environment, with mechanical agitation in a Medtronic pump reservoir and at temperatures of 37°C.[14] This temperature might be exceeded in direct sunlight. All Medtronic pumps have a transparent window to show the amount of insulin in the reservoir, and the infusion sets are also transparent, but insulin is not usually degraded to the extent of losing its potency during exposure to sunlight in daily use. Therefore heat, rather than sunlight, probably reduced the effectiveness of the insulin. Hyperglycaemia secondary to exposure of insulin to direct sunlight and high temperatures has been described in a mountain climber.[15]

Patients with diabetes should participate in regular exercise as part of healthy lifestyles, but if an insulin pump is disconnected during such activities, it should be placed away from sunlight and extreme temperatures.[16] If hyperglycaemia occurs despite a corrective dose of insulin and changing the infusion set, the insulin in the reservoir should also be changed; in our case, the medical team did not detect the omission of this step, causing a delay in attainment of normoglycaemia. This advice is included in the continuing education of patients in diabetes clinics, but it is also something all clinical staff who may care for patients with diabetic ketoacidosis in an emergency setting need to be aware of.

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Patient consent obtained.

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Towards earlier diagnosis of dementia

I have often benefited as a GP from remembering the dictum "If you start to feel low in spirits during a consultation the patient may be suffering from depression." I would like to coin another dictum: if you start to feel confused during a consultation, the patient may be suffering from early dementia.

To explore this idea further, I surveyed the 30 patients with a new diagnosis of dementia made over the past year from our practice list in a retirement town of 4455 patients aged over 70. I compared their consultation rates and "DNA rates" (missed appointments) in the two years preceding diagnosis with the average consultation and DNA rates for all our patients over 70 years old. I found that both rates were double among the new cases compared with the average for the age group.

I then compared the medical records of the patients with a new diagnosis of dementia against the records of two patients matched for age, sex, general practitioner, and place of residence (that is, own home, residential care, or nursing home). I found that the patients later diagnosed with dementia were not consulting about their memory, but more frequently than average about routine medical matters such as ear wax, constipation, etc.

It would seem that a change in consulting behaviour may be an early sign of the onset of dementia, so when you start to ask yourself, "Why is he/she back about this again?" think about possible memory loss.

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