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The Sri Lanka Prescriber

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Cover picture

MONASTIC PHARMACY (5th to 12th centuries)

Monks, trained as apothecaries, preserved and advanced pharmaceutical knowledge during the Middle Ages; raised medical herbs in cloister gardens for treatment of the ill and injured in their care.

One of a series: *A History of Pharmacy in Pictures*, presented by Parke, Davis & Company.

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Carbamazepine related Stevens-Johnson syndrome and toxic epidermal necrolysis. Genetic testing to identify patients at risk

ADR Corner

We recently received an Averse Drug Reaction (ADR) report of Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) overlap syndrome after commencement of carbamazepine. The patient was a four-year-old girl of Sinhalese ethnicity, who developed SJS/TEN 18 days after carbamazepine was started for frontal lobe epilepsy with rapid secondary generalization. She was admitted to a tertiary care teaching hospital and carbamazepine was promptly withdrawn. She has survived this severe ADR with appropriate supportive therapy.

This ADR was selected for publication as there are recent advances in the ability to identify patients who are at risk of developing SJS/TEN through genetic testing.

This paper attempts to describe available methods to predict and prevent SJS and TEN related to carbamazepine.

Introduction

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) fall within the spectrum of severe cutaneous adverse reactions (SCAR) to medicines [1]. They are considered to be two diseases within a single continuum, characterised by the extent of body surface area (BSA) affected by epidermal detachment; >30% in established TEN, 10-30% in SJS/TEN overlap syndrome, <10% in SJS, are the extent of mucosal involvement. SJS/TEN may also show other organ involvement, and have a mortality rate as high as 30% [2,3]. SJS/TEN generally occurs with an exposure to a medicine. However, the culprit medicine is identified only in 75% of the cases [3,4].

According to data from RegisSCAR/EuroSCAR registry, carbamazepine is a high-risk medicine causing SJS/TEN [5]. A case control study done in Europe found carbamazepine to have the highest multivariate risk compared to other antiepileptics causing SJS/TEN [6]. The estimated risk with carbamazepine is 1 to 10 per 10000 new users for Caucasians [7,8] and it is reported to be ten times higher for Asians [7]. Sodium valproate, on the other hand, has shown consistently low risk of causing SJS/TEN [8,9].

Genetic susceptibility

If such serious adverse effects to medicines are to be

prevented, we need to identify a reliable predictor of occurrence. Over the past decade advances in pharmacogenomics has revealed several human leukocyte antigens (HLA) alleles to be associated with significantly increased risk of SCARs. Most of these genetic risk factors are drug and ethnicity specific [10].

HLA-B*1502 was first found to be associated with increased risk of carbamazepine induced SJS in Han Chinese in 2004 [11]. Subsequently, it was found to have the same association in several other Asian populations including Thais [12], Malays [13], Indians [14] and Cambodians [15]. However, Caucasians with HLA-B*1502 did not have an increased risk of SJS/TEN. There are several other HLA alleles that are associated with increased risk in different populations. These include HLA-B*1511 and HLA-A*3101 in Japanese [16] and Koreans [17], and HLA-A*3101 in Europeans [18]. In addition to the above, many other alleles belonging to the same family as HLA-B*1502 (e.g. HLA-B*15:08, B*15:11, B*15:18 and B*15:21) have been found in different individuals with SJS/TEN from different ethnicities, mostly of Asian ancestry [10].

Pharmacogenetic screening

Avoiding carbamazepine in patients who have these alleles could be effective in preventing carbamazepine related SJS/TEN. Several case control studies provide strong evidence to support the use of genotyping of HLA-B*1502 as a pharmacogenetic screening test in patients with Asian descent. Furthermore, it has been found to have a sensitivity approaching 100% [12,19]. However, the place of HLA-A*3101 genotyping in Caucasians and genotyping of other alleles is yet to be determined.

Based on these findings the United States Food and Drug Administration (FDA) recommended in 2007 HLA-B*1502 testing before starting carbamazepine in Asians [7]. Since then, HLA testing has been made mandatory in Hong Kong and Taiwan. In 2008, the UK Medicines and Healthcare products Regulatory Agency (MHRA) and the Commission on Human Medicines (CHM) recommended screening for HLA-B*1502 in individuals with Han Chinese, Hong-Kong Chinese and Thai descent and extended this recommendation to all individuals with an Asian ancestry in 2012 [18]. In 2013, Singapore adopted pharmacogenetic screening before carbamazepine therapy as their recommended standard of care. All these authorities advocate avoiding carbamazepine in individuals positive

for HLA-B*1502 and using an alternative antiepileptic medicine.

Advantages

Since the introduction of HLA allele screening, several studies across the region have looked into its utility and cost-effectiveness. A study in Thailand that compared the cost-utility of universal HLA-B*1502 screening versus a policy of prescribing a medicine other than carbamazepine for epilepsy or neuropathic pain found both interventions to significantly decrease the number of carbamazepine related SJS/TEN cases [20]. However, universal HLA-B*1502 screening was preferable over the other because it was far less expensive. Furthermore, this study revealed that 343 patients need to be tested for the HLA-B*1502 allele to prevent one case of SJS/TEN. It concluded that a program of universal HLA-B*1502 screening is good value for the money when conducted on patients with neuropathic pain, but not for patients with epilepsy. This was due to switching to a more expensive alternative treatment for epilepsy as a precautionary measure in those who test positive for the allele.

Comparable to the Thai findings, another study in Singapore found that genotyping for HLA-B*1502 and providing alternate antiepileptics to those who tested positive was cost-effective for Singaporean Chinese and Malays, but not for Singaporean Indians [21]. These findings were attributed to the different population allele frequencies. A study in Hong Kong claims that screening for HLA-B*1502 has comparable efficiency and cost-efficiency as mammography to prevent breast cancer or PAP smear to prevent cervical cancer [22].

The consensus is that pharmacogenetic screening before carbamazepine therapy is cost-effective and efficient. But in any population such conclusions must be based on the population frequency of HLA-B*1502, the positive predictive value of the test, duration of treatment relative to life expectancy, costs of alternative drugs and the cost of treatment of SJS/TEN and its long term sequelae.

Limitations

Pharmacogenetic testing for HLA-B*1502 is not completely devoid of limitations. One major unanswered question is whether other aromatic anticonvulsants (i.e. lamotrigine, phenytoin, oxcarbazepine) should also be avoided in those who test positive for HLA-B*1502. Although some case-control studies have found HLA-B*1502 in patients with SJS/TEN related to the above antiepileptics [23], the answer to this question is yet to be determined.

Moreover, the association of HLA-B*1502 does not hold true in some parts of East Asia such as Korea and Japan.

The Asian or South-east Asian ancestry is also becoming increasingly difficult to define with the growing number of inter-ethnic marriages. Furthermore, there are reports of carbamazepine related SJS/TEN in patients negative for HLA-B*1502 from East and South-east Asia [15]. Therefore other factors that cause SJS/TEN in HLA-B*1502 negative patients such as viral infections and mycoplasma pneumonia infection [3] are also likely to exist conferring less than 100% protection in those who become negative in screening.

The Sri Lankan perspective

The allele frequency of HLA-B*1502 is approximately 1-8% in the South-east Asian countries [15]. A study done with 93 healthy Sri Lankans has found an overall HLA-B*1502 allele frequency of 4.3%. They report an ethnicity based carrier frequency of 9.3% for Sinhalese and 3.2% for Moors and 0% for Tamils [24]. These findings are comparable to another study done in 185 female Tamils of Indian origin in plantations in whom the HLA-B*1502 allele has been found to be rare [25]. Further studies are needed to verify these figures and to determine the allele frequency in different regions of the country.

The reported incidence of SJS and TEN in Asia is 8 per million person year, as compared to 0.4-7.4 per million person year in Caucasian populations [15]. Of these reported cases 25%-33% are related to carbamazepine. In Sri Lanka, the incidence of SJS/TEN or the proportion of it related to carbamazepine is not known. This lack of data stems from a problem of much bigger magnitude; extreme under-reporting of all ADRs in the country.

Hence, we are at a dual disadvantage. We do not know the magnitude of the problem nor the genetic risk associated with it. Although infrequent, these conditions can be fatal or severely disabling. So we urge the medical community to assist in pharmacovigilance, through reporting of ADRs as it would help in providing data on magnitude of the problem, which would help in implementing prevention strategies.

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Rational use of topical corticosteroids

Summary

Many dermatological conditions will respond to a topical corticosteroid. The clinical outcome will depend on making a correct clinical diagnosis and applying the right molecule in the most appropriate vehicle for the correct duration.

Topical corticosteroids are classified by their strength, but the same molecule will have different effects depending on the vehicle. The patient's age and the affected area of skin are other important factors.

If used correctly the adverse effects of topical corticosteroids are usually minimal. Systemic effects can occur with high doses.

Key words: atrophy, cream, ointment, pregnancy, vehicle

(*Aust Prescr* 2013; **36**: 158-61)

Introduction

Skin conditions represent 10% of the problems managed in general practice,¹ and many inflammatory skin diseases are treated with topical corticosteroids.² Before prescribing a topical corticosteroid it is important to be certain of the diagnosis as the drugs exacerbate some conditions, such as tinea. Topical corticosteroids may be underused or overused, so it is important that the patient knows what the treatment is and how it should be applied.

Molecules and vehicles

There are many topical corticosteroids which are available in a variety of strengths and in different vehicles. The classification of topical corticosteroids was based on how much vasoconstriction they cause and on some comparative clinical trials. The USA classification ranges from Class 1 (most potent) to Class 7 (least potent), whereas the UK classification has four different categories (Table). The Australian Medicines Handbook and Therapeutic Guidelines class topical steroids as mild, moderate, potent and very potent, while the Schedule of Pharmaceutical Benefits lists them as weak, moderately potent and potent.

Topical preparations may have the same or similar active compound but differ in their concentration or vehicle, which ultimately affects their potency, absorption and efficacy. As an example, betamethasone dipropionate 0.05% is found

in a number of categories. By changing its vehicle from a cream to an ointment its potency increases from moderate to potent (UK category III to II), and when it is delivered in an optimised vehicle it becomes very potent (category I). In general, ointments improve the drug's penetration as they occlude the skin and enhance hydration and absorption. However, ointments are greasy and difficult to spread. This is sometimes an important reason for a patient's poor adherence to treatment. Creams are a combination of one or more nonmixable liquids and an emulsifying agent. They are less greasy than ointments, very easy to spread and are washable in water.

Lotions are insoluble preparations dispersed into a liquid. They may need shaking to get the mixture ready for use, but are easy to apply, can cover extensive areas and are preferred for children (due to their more permeable skin) and on hairy skin.⁵

Mechanism of action

Topical corticosteroids act by binding to a specific receptor in the cellular cytoplasm and modulating the transcription of multiple genes. This leads to the suppression of the production of inflammatory substances such as prostaglandins and leukotrienes, and also inhibits the recruitment of inflammatory cells into the skin.

Adverse effects

Although topical corticosteroids are relatively safe, they can produce local (more frequent) and systemic (infrequent) adverse effects when used incorrectly.⁶ High potency topical corticosteroids should not be used on areas of thin skin (for example face, flexural sites, scrotum, eyelids) as absorption is increased. They should not be used on denuded skin or for longer periods. Caution is needed if these drugs are used under occlusion, in children or in elderly patients.

Local effects

Atrophy of the skin is one of the most common cutaneous adverse effects. There is an increase in skin transparency and brightness, telangiectasia, striae and easy bruising. Scars and ulceration may appear due to dermal atrophy. The use of topical corticosteroids on the face can induce eruptions such as steroidal rosacea, acne and perioral dermatitis.

Less frequent local adverse effects include hypopigmentation, delayed wound healing and glaucoma when corticosteroids are applied around the eye. Contact

Table. Classification system for commonly used topical corticosteroids^{3,4}

	Presentations available		
	Ointment	Cream	Lotion
Superpotent – Class 1 USA, Class I UK			
Betamethasone dipropionate 0.05% in optimised vehicle	X		
Clobetasol propionate 0.05%	X		
High potency – Class 2/3 USA, Class II UK			
Betamethasone dipropionate 0.05%	X		
Betamethasone valerate 0.1%	X		
Mometasone furoate 0.1%	X	X	
Moderate potency – Class 4/5 USA, Class III UK			
Betamethasone dipropionate 0.05%		X	X
Betamethasone valerate 0.05%	X	X	
Triamcinolone acetonide 0.1%		X	
Methylprednisolone aceponate 0.1%	X	X	X
Clobetasone 0.05%		X	
Low potency – Class 6/7 USA, Class IV UK			
Hydrocortisone or hydrocortisone acetate 0.5%, 1%	X	X	X
Desonide 0.05%	X	X	X

sensitivity to preservatives in the product or the corticosteroid itself may occur and clinically it can be suspected by persistence or worsening of the skin disease.

Other adverse effects include:

- disease recurrence due to a rebound effect when treatment is stopped
- tachyphylaxis or loss of clinical improvement after a period of use (although frequently reported, it has not been observed in clinical trials)
- masking or stimulation of some cutaneous infections (for example tinea incognita)

Systemic effects

Systemic adverse effects are uncommon and are mostly associated with the use of high potency topical steroids in large or denuded areas, under occlusion or in severe skin disease. Reversible suppression of the hypothalamic-pituitary-adrenal axis has been described in children with doses as little as 14 g per week. Moreover, stopping therapy may induce an Addisonian crisis. Other systemic effects include Cushing's syndrome, diabetes mellitus and hyperglycaemia.

Recommendations for topical corticosteroid use

Establishing a diagnosis is essential to choosing the appropriate topical corticosteroid. Once a diagnosis has been made, several considerations influence the choice.^{5,7} It is also important to ask if the patient has already been using an over-the-counter topical corticosteroid.

Disease responsiveness

On thin skin, inflammatory skin conditions like intertriginous psoriasis, children's atopic dermatitis, seborrhoeic dermatitis and other intertrigos are highly responsive and will respond to a weak topical corticosteroid. Psoriasis, adult atopic dermatitis and nummular eczema are moderately responsive diseases so require a medium potency corticosteroid. Chronic, hyperkeratotic, lichenified or indurated lesions, such as palmo-plantar psoriasis, lichen planus and lichen simplex chronicus, are the least responsive diseases and require high potency topical corticosteroids.⁵

As a general rule, topical corticosteroids should not be used in patients with rosacea, perioral dermatitis or acne. Skin infections are also a contraindication.

Location

The anatomical site, specific characteristics of the stratum corneum and skin lipid structure affect the penetration and absorption of topical corticosteroids. For example, absorption on the palms, soles (0.1-0.8%) and forearms (1%) is poor, compared to the face (10%), scalp and intertriginous areas (about 4%). Other areas such as the scrotum and eyelids will absorb up to 40% of applied drugs. Potent topical corticosteroids and prolonged use of lower strength topical corticosteroids should be avoided in these areas.

Dermatoses of the face and intertriginous areas are best treated with low-strength preparations. Lesions on the palms and soles frequently require treatment with high potency topical corticosteroids. If the affected area is large, use low to medium potency corticosteroids to reduce the likelihood of systemic effects.

Vehicle

Although ointments are generally the most effective vehicle for treating thick, fissured, lichenified skin lesions, patients may consider them cosmetically unappealing. Ointments should not be used in flexural or intertriginous areas due to high absorption. Creams are generally well accepted on most areas of the skin except the scalp.

Lotions are useful for extensive areas, while solutions, gels, sprays and foams are useful for the scalp and hairy skin. These products can produce irritation when applied to acute dermatoses.

Amount

A single application to the whole body of an adult will require 30 to 40 g of product. An area of one hand (palm and digits) will require 0.3 g per application. No more than 45 g/week of potent or 100 g/week of a moderately potent topical steroid should be applied if systemic absorption is to be avoided. In children, the amounts should be smaller.

Frequency of application

This depends on the selected topical corticosteroid and the site to be treated. Application once or twice daily is usually sufficient, but frequency may increase when treating areas where the preparation can easily be wiped off (for example palms and soles). Treatment under occlusion should be avoided and only prescribed by specialists familiar with the use of corticosteroids and the condition to be treated.

Treatment duration

The shortest course of treatment is recommended for acute diseases, although small recalcitrant lesions may need to

be treated for longer. Treatment should not be longer than two weeks on the face and 3-4 weeks on the rest of the body. For longer treatment periods, intermittent therapy such as every other day, weekend-only application or a resting period of 1-2 weeks between cycles may be an option. Very short treatments (1-3 days) will not provide enough improvement of some conditions and this may be wrongly interpreted as unresponsiveness.

Children

Children, especially infants, are more susceptible to adverse effects. They have difficulty in metabolising potent corticosteroids and their skin surface area: body weight ratio increases systemic absorption. Topical treatment in children should be used with extreme caution. Prescribe a low potency corticosteroid and preferably for short periods. An application under occlusion in the nappy area or under plastic should be avoided.

Pregnancy and lactation

All topical corticosteroids are classified category C by the US Food and Drug Administration, but some are classified category A by the Therapeutic Goods Administration (www.tga.gov.au/hp/medicines-pregnancy.htm). Studies in animals have shown that topical steroids are systemically absorbed and may cause fetal abnormalities. Limited and inconclusive data are available for humans, however there seems to be an association between very potent topical corticosteroids and fetal growth restriction.^{8,9}

Caution is needed, but topical corticosteroids have been frequently used in pregnancy. Although the mechanism of topical corticosteroid excretion in breast milk is unknown, there are no reported adverse effects during lactation. These drugs should not be applied directly to the nipples before breastfeeding.

Adjunctive treatments

Patients should be given advice about skin care. This includes the use of soap-free cleansers and moisturiser which will affect the skin's overall integrity and improve the clinical outcome.

Conclusion

Topical corticosteroids are safe and effective drugs. Always establish a clinical diagnosis before prescribing. Choose an appropriate topical corticosteroid according to the affected area, patient's age, clinical presentation and predicted responsiveness to treatment.

Monitor the clinical response, even if symptoms have resolved. Consider changing or even stopping treatment according to the response. Also monitor for adverse effects and cease the drug straight away if there is skin damage.

Refer to a dermatologist if the disease does not respond to treatment or when the diagnosis is unclear.

Conflict of interest: none declared

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Type 2 diabetes in older people, challenges in the management

The known prevalence of diabetes mellitus in Sri Lanka for those above the age of 20 years is 10.9% [1]. This diabetic population is predicted to increase by 31 000 cases per year with a projected 2.158 million suffering from diabetes by the year 2030 [2,3]. The prevalence progressively increases with age in both men and women, with the highest prevalence reported in individuals above the age of 70 years [1]. The International Diabetes Federation (2013) considers people aged 70 years and above as “older people” and categorises them into functionally independent, functionally dependent either frail or with cognitive impairment, and people receiving end of life care [4].

The glycaemic targets for control in these categories of older people are:

1. HbA1c 7.0 - 7.5% in functionally independent
- 2A. HbA1c 7.0 - 8.0% in functionally dependent who are fit with satisfactory cognitive function
- 2B. HbA1c up to 8.5% in functionally dependent who are frail and with associated dementia
3. No target HbA1c, but symptomatic hyperglycaemia to be avoided in those receiving end of life care

Treating diabetes in the older population is a challenge for many reasons, and calls for a hands-on approach. The following case histories are intended to emphasise the principles of management of diabetes in older people.

Case history 1 – preventing hypoglycaemia

A 72-year old man has been a diabetic for 10 years, currently on metformin monotherapy at 750mg with the 3 main meals. He was found to have poor blood glucose control over 2 months with a HbA1c of 11.1%, (fasting blood glucose 190-200mg/dl, 2 hour post-prandial blood glucose > 200mg/dl) despite good adherence to therapy (Table 1) and the diet. A secondary cause or use of other medications that could have contributed to the hyperglycemia could not be identified. He was also on isosorbide mononitrate for angina. His liver function and renal function were age appropriate.

What additional antidiabetic medication should be added at this stage and in what dosage?

It was decided to add 125mg of tolbutamide, a short-acting

Panel 1. Challenges of type 2 diabetes in older people [4]

- Associated comorbidities and multiple drug therapy leading to poor adherence.
- Poor adherence, adverse effects of medications and drug interactions causing poor blood glucose control.
- Hyperglycaemia leading to complications of diabetes as in adults.
- High risk of hypoglycaemia associated with renal dysfunction, use of insulin / sulphonylurea, irregular timing of meals, inadequate food intake, living alone/ inadequate support.
- Hypoglycaemia increases the risk of cardiovascular disease and falls.
- Medication errors associated with visual impairment, hearing defects, impaired dexterity and forgetfulness.

sulphonylurea, with all 3 meals as both fasting blood glucose (FBG) and post-prandial blood glucose values were high throughout the day. The patient's daughter was advised to monitor blood glucose at home using a glucometer. Metformin was continued at a dose of 750mg with all 3 meals. No major dietary modifications were done. However, taking fruits as mid-morning or mid afternoon snacks, and avoiding mealtime fruits and fruit juices were emphasised.

On the 5th day of combined therapy (day7) his blood glucose values were: fasting 141mg/dl, post-breakfast 214 mg/dl, pre-lunch 112, and post-lunch 137mg/dl. He was advised to continue with the same treatment and monitor blood glucose at 3-4 points every week while adhering to therapy and a consistent diet which was supervised by his wife and daughter. Blood glucose values in the second and third week of treatment are given in Table 2.

What are the concerns regarding his blood glucose values on day 21? What action is required regarding his antidiabetic medications?

Since his pre-lunch and post-lunch blood glucose values

Table 1. Blood glucose before and after adding tolbutamide

Day	Blood glucose measurements (mg/dl)						Treatment
	FBG	Post-BF ^a	Pre-lunch	Post-lunch	Pre-dinner	Post-dinner	
Day 1 (3.02.2015)	195	220	201	224	257	293	Metformin 750mg with all 3 meals
Day 2	204	304	166	231	189		Tolbutamide 125mg with all three meals added from Day 3
Day 7	141	214	112	137	-	-	Same regime continued

^aBreakfast, FBG (capillary blood glucose)

Table 2. Blood glucose during the 2nd and 3rd week of treatment

Day	Blood glucose measurements (mg/dl)						Treatment
	FBG	Post-BF	Pre-lunch	Post-lunch	Pre-dinner	Post-dinner	
Day 14	136	183			105		Metformin 750mg and tobutamide 125mg with all three meals continued
Day 21	111		88	119		157	

Table 3. Long term blood glucose measurements in the 3rd – 12th week

Day	Blood glucose measurements (mg/dl)						Treatment
	FBG	Post-BF	Pre-lunch	Post-lunch	Pre-dinner	Post-dinner	
Day 22	105		103	153			Reduce metformin to 250 mg with breakfast and 500 mg with lunch and dinner, tolbutamide to 125 mg with breakfast only
Day 24	124						
Day 27			113	183			Continuing same
5 th week			113				
9 th week		149			99		
11 th week	143		168				
12 th week	129		124		119		

were low, priority was given to preventing hypoglycaemia. Therefore, from the third week onwards it was decided to reduce the dose of metformin to 500mg with breakfast and dinner and to omit the lunch time dose of tolbutamide (125mg) while continuing with metformin 750mg with lunch. Two days later (day 23) his morning fasting blood glucose (FBG) was reported as 105 mg/dl at 6 am.

What immediate action should be taken now?

With these blood glucose values there is a clear trend of declining fasting blood glucose. When the FBG is low, we would expect the values throughout the day to be lower than previously reported (pattern recognition). Therefore, due to the imminent risk of hypoglycemia, at pre-lunch, advice was given to immediately reduce the morning dose of metformin to 250mg and the lunchtime and nighttime doses were also reduced to 500 mg. Tolbutamide 125mg

with breakfast was continued and the tolbutamide dose given with dinner was omitted, as the FBG was low. Following this change, his pre-lunch blood glucose (BG) became 103mg/dl and post-lunch was 153 mg/dl. Thereafter, the blood glucose profile was monitored for 2 days and the patient and family were instructed to repeat measurements weekly or once in 7-10 days (Table 3).

At this stage his glycaemia was well within targets for control with the treatment regimen and monitored with 2-3 point capillary blood glucose measurements once in 3 weeks.

Principles of management

1. Prevent hypoglycaemia

There is a higher risk of hypoglycaemia in older people

from multiple factors, including their ability to recognise and respond to hypoglycemia is limited due to age-related impairment of counter-regulatory processes [4]. Added insulin or sulphonylurea therapy is known to cause hypoglycaemia especially in older people. About 50% of older patients with type 2 diabetes have undiagnosed renal impairment, which further increases the risk of hypoglycaemia. Irregular timing of meals and inadequate food intake add to the risk. Food intake may be reduced due to loss of appetite, taste disturbances related to medications or sometimes as a result of poor oral hygiene.

Hypoglycaemia increases the risk of cardiovascular disease and serious events such as falls, hip and lower limb fractures, and traumatic intracranial haemorrhage. It increases all cause hospitalisation and all cause mortality. Hence the risk factors should be identified early to educate the patient and the care-givers to prevent hypoglycaemia and its consequences.

Notes:

- a. Antidiabetic medications should be prescribed at the lowest effective dose to minimise gastrointestinal adverse effects with metformin, and hypoglycaemia with sulphonylureas or insulin. Older people are very sensitive to medications, especially when blood glucose is nearly normal, when compared with when blood glucose is high [5, 6].
- b. Close monitoring and dose adjustment is necessary when initiating or adding antidiabetic medications or changing doses. While aiming at blood glucose targets for control, doses should be decreased at points that show a trend towards hypoglycaemia. Those on metformin and sulphonylurea combination therapy or metformin monotherapy with either drug too need particular attention although hypoglycaemia is very rare with metformin monotherapy.

2. Dose adjustments to achieve target glycaemic control

In older people, the challenge in maintaining targets for control is to prevent hypoglycaemia while ensuring adequate blood glucose control. FBG and pre-meal blood glucose should be maintained closer to the upper limit; FBG 80-130mg/dl, and post-meal blood glucose <180mg/dl or < 200mg/dl with increasing age. HbA1c% needs to be maintained between 7.00-7.5% in functionally independent and 7.5-8.5% in those who are functionally dependent, frail or with cognitive impairment, to prevent long term complications [4]. These targets should be achieved in older people gradually by titrating the antidiabetic medication doses.

Notes:

- a. The dose adjustment should be started at a point low blood glucose is observed at fasting, pre-meal or 2 hour post-meal. Whatever the timing, the dose at the meal prior to blood glucose testing should be adjusted after excluding any change in the quantity of the meal before testing. This is mainly to prevent hypoglycaemia, and subsequent dose adjustment is necessary to prevent hyperglycaemia. Blood glucose measurements at different time points of the day are useful to decide on the appropriate dose with each meal.
- b. In this case history, blood glucose targets have been reached with a total daily dose of 1,250mg of metformin and only 125mg of tolbutamide daily with asymmetrical dosing. Asymmetrical dosing may be required to match the post-prandial blood glucose response after each meal to achieve the targets, and to avoid hypoglycemia.

Panel 2. Action plan when blood glucose is high

Test capillary blood glucose at 3-4 points

- Identify the time points where blood glucose is high. Identify and treat any occult infection (infected foot ulcer, gingivitis/periodontitis)
- Identify poor adherence to therapy: ask the patient
 1. “How many doses are usually missed during a day or week”?
 2. “Do you take a different dose instead of the prescribed dose either to prevent adverse effects or improve efficacy”?
 3. “What time do you take the prescribed drug doses for your convenience or the convenience of your family member or care-giver? Is this time consistent or does it change day by day?”
- Check whether blood glucose is low at any time point. Identify the pattern of blood glucose variation.
- First correct or prevent hypoglycaemia before attending to high values.
- Check whether the medication before testing was taken correctly (the dose and the time) Example; if metformin was taken 1 hour after the meal, the timing is incorrect and may result in high post meal-blood glucose.
- Check on the quality and the quantity of the previous meal or snacks eaten by the patient prior to blood glucose testing; are they according to the recommendations?

3. Dietary modifications

Dietary restrictions should be minimised, but fruit juices and other sugary drinks should be avoided. A fruit or a portion of a fruit or an unsweetened or mild to moderately sweetened snack is recommended 2-3 hours after breakfast and lunch. This prevents mid-morning and mid-afternoon hypoglycaemia. Fruits should be avoided immediately after a main meal to prevent post-meal hyperglycaemia. Carbohydrate intake should be consistent and meal plans should be individualised considering patient's preferences, eating routines and general health status [4].

Notes:

- a. Regular meal times are necessary as antidiabetic medications are taken with the main meals. Regular snacks prevent pre-meal hypoglycaemia. A fruit as a snack prevents pre-meal hypoglycaemia and fulfills the above requirement as well.
- b. Many cups of unsweetened plain tea as required are encouraged with the snacks as it helps to keep older people well hydrated. Avoid tea following main meals as the tannin in tea tends to bind to dietary iron.
- c. Fruit juices should be avoided. Moderately sugary snacks may be allowed at social events once blood glucose and HbA1c% have reached targets for control and the BMI and waist circumference are within safe limits.

4. Concomitant use of other medications

Many older individuals have comorbidities and are on several medications. Physicians should take a comprehensive medication history to safely and effectively manage diabetes, and to avoid possible drug interactions. Example: angiotensin converting enzyme (ACE) inhibitors

are known to potentiate the effects of antidiabetic medications.

Case history 2 – commencing therapy with the lowest effective dose

A 72-year old woman with type 2 diabetes who presented with a UTI was found to have poor blood glucose control. Her FBG was 230mg/dl and HbA1c was 8.8% at presentation. She did not have any evidence of long term complications of diabetes. She had been diagnosed with diabetes 2 years ago, and was initially treated in hospital with insulin and sitagliptin. Insulin had been discontinued on discharge, and metformin prescribed with sitagliptin. The patient had refused to continue with sitagliptin as she found it to be expensive, costing Rs. 250/- per tablet. Subsequently, she had been prescribed metformin 500mg three times a day. With the first tablet of metformin she had developed severe nausea and had discontinued the medication. Following this she had been commenced on tolbutamide 250mg daily with lunch. However, she had discontinued tolbutamide too on her own, as she had experienced hypoglycaemic symptoms and had frequently noted capillary glucose to be less than 80mg/dl.

What antidiabetic medication should be prescribed for her?

After discussing and convincing the patient that side-effects of metformin would be minimal if started on a low dose, she agreed to start on 125mg of metformin. Two days later (day 3), the dose was increased to 250mg with breakfast and lunch due to persistently high post-breakfast and post-lunch values. On day 6, metformin 125mg was added with dinner as her FBG was still high. She did not develop nausea or any other gastrointestinal adverse effect with these doses. Gradually blood glucose control improved on the same regimen (Table 4).

Table 4. Blood glucose control over the first 5 weeks

Day	Blood glucose measurements (mg/dl)						Treatment
	FBG	Post-BF	Pre-lunch	Post-lunch	Pre-dinner	Post-dinner	
Day 1	230	277					Started metformin 125mg with breakfast and lunch
Day 2		259		258			Increased metformin to 250mg with breakfast and lunch
Day 3		239		232			
Day 6	161	268		173			Metformin 125 mg added with dinner
Day 10	130	221		157			Morning dose of metformin increased to 375mg. Lunch time metformin dose reduced to 125 mg
Week 5	125	160		126			Lunch time metformin discontinued.

However, her post-breakfast BG was consistently high even on day 10 and the post-lunch glucose was comparatively low. Therefore, the dose of metformin with breakfast was increased by 125mg and the dose of metformin with lunch was reduced by 125mg and later discontinued, maintaining her on a total daily dose of only 500mg of metformin with asymmetrical dosing (375mg with breakfast and 125mg with dinner) to match the post-meal glucose response at different meal times.

Principles of management

5. Avoid adverse effects of medication

Antidiabetic medication should be started at low doses. The dose and frequency should be adjusted according to blood glucose response. Oral antidiabetic medications should be taken strictly with meals or soon after meals, emphasising avoidance of taking before meals. Medications started on high doses increase the risk of adverse effects and non-adherence to therapy.

6. Home blood glucose monitoring

Blood glucose should be monitored frequently at least once a week (1-2 FBGs and 2 post-prandial blood glucose at different meal times) during the first month of initiating or changing therapy. The values should be discussed with the patient or care-giver. They should also be educated on the action to be taken with low or high values.

Notes:

- a. When interpreting blood glucose done at different points of the day, it should be matched with the meal taken before blood glucose testing. If a high post-meal value results from an unusually large meal or a sugary snack that has been taken by the patient deviating from the usual diet, appropriate dietary advice with an emphasis on a consistent diet would suffice. Dose adjustments should be considered with high or low values if they are not due to a change in the diet or any other factor. If the blood glucose is high in association with an infection the adjusted dose should be reviewed once the infection resolves.

Discussion

The altered pharmacodynamics and pharmacokinetics of medications, impaired physiological compensatory mechanisms and many social factors alter older patients' response to medications and incidence of adverse effects. Concomitant use of other medication for comorbidities adds another concern. The physician should select medications after taking a comprehensive history and examining the patient, considering all the factors mentioned above. Treatment should be started with the lowest effective dose as monotherapy. Metformin is the

recommended first-line drug unless there is a contraindication. The dose increments should be based on the blood glucose values. Hence monitoring blood glucose 3-4 times a day initially, and later 2-3 measurements once in 3-4 weeks are necessary to ensure control targets of control.

The patient and the caregivers should be educated on the advantages of frequent blood glucose monitoring especially during initiation or change of therapy. When interpreting blood glucose results, it is essential to match it with the main meal and snacks taken prior to blood glucose testing. Non-adherence to therapy too should be excluded before changing the dose. The patient and the caregivers should be introduced to the Diabetic Educator Nurses who are available in General Hospitals and Base Hospitals to give advice on any difficulties in the management of blood glucose.

Monitoring fasting blood glucose alone is inadequate to optimise blood glucose control. Post-meal blood glucose, both post-breakfast and post-lunch are essential for individualising therapy and preventing adverse effects associated with inappropriately high doses of medication. A short-acting sulphonylurea (SU) metabolized in the liver (tolbutamide or gliclazide) is preferred in older people, if there is no liver impairment. Glibenclamide, which is a long-acting SU excreted through the kidneys, should be avoided in older people and in those aged > 60 years (7). Glipizide, too should be avoided, although it is metabolised in the liver, as it is a long-acting SU.

If blood glucose control cannot be achieved with metformin and a SU, a small dose (4-6 units) of an intermediate acting insulin (isophane insulin) should be added with breakfast to control the meal related blood glucose rise during daytime. Very rarely there may be a need to change to premixed insulin once or twice a day. The insulin pen is preferred (31 G, 5mm needles) for patients who can afford it, if not an insulin syringe with a fixed 30G and <8mm length needle should be used as longer needles are likely to pierce the muscle during subcutaneous administration especially in males [8]. Furthermore, longer needles cause more pain leading to poor adherence to the insulin regimen [9].

The number of medications should be kept to a minimum to prevent medication errors and related hypoglycaemia. The risk of hypoglycaemia with medication is high in the older population with diabetes. Physical activities such as gardening or long distance walking should be avoided close to mealtimes or at times known to have low blood glucose values. Avoiding hypoglycaemia should be a primary objective of managing older people with diabetes. Frequent hypoglycaemia would give a falsely low value of HbA1c% and increase the risk of hypoglycaemic unawareness.

Medication errors are common in older people. Visual impairment, hearing defects and impaired dexterity contribute to errors. The care-givers should be advised to supervise or frequently review medicine intake or use strategies to improve medicine adherence such as a pill-box or a drug chart (to tick off after taking each medication). During a consultation it is important to request the presence of a family member or the caregiver too. A summary of the instructions should be given in writing in their preferred language. The patient or caregiver may record the instructions in a mobile phone as this facility is available readily to many in Sri Lanka.

Dietary restrictions should be minimised and the need for a consistent dietary pattern should be emphasised. The patient's medication and food intake should be supervised and reviewed frequently by a family member or caregiver and any issues should be discussed with the diabetic educator nurse or the physician. Sugar substitutes are not encouraged. Diabetic powdered drinks containing fructose should be avoided as these are known to increase serum triglyceride levels and lead to fatty liver [10].

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Self-assessment questions

Question 1

A 68-year old male retired civil engineer a non-smoker and teetotaler, was admitted to NHSL with a 2-month history of dyspnoea on mild exertion, 7 kg weight loss, increasing muscle weakness, and loss of appetite. There was no significant past history. On examination he was pale, with bilateral ankle oedema, a blood pressure of 195/105 mmHg, pulse rate 88 bpm, and respiration rate of 18 per minute at rest. Rest of the clinical examination was normal except for marked muscle wasting and a BMI of 18.5. The following test results were received within 24 hours.

Hb	9.5 g/dl	(14.0 – 17.5)	Na	147 mmol/l	(135 – 145)
MCV	86 fl	(80 – 96)	K	2.5 mmol/l	(3.5 – 5.0)
MCHC	359g/dl	(320 – 360)	Urea	6.8 mmol/l	(2.5 – 6.5)
WCC	7.2 X 10 ⁹ /l	(4 – 11)	Creatinine	76 µmol/l	(60 – 120)
CRP	45 g/l	(< 5 g/l)	*Glucose	6.6 mmol/l	(4.5 – 5.6)
ESR	78	(<20)	Bilirubin	20 µmol/l	(3 – 17)
			ALT	46 U/l	(5 – 40)
			(* Fasting)		

1. What is the most likely diagnosis at this stage?
2. List 5 investigations that will help to confirm your diagnosis.

Question 2

A 75-year old man is admitted to hospital with a ten day history of fever with diarrhoea, occasional chills and rigors, and pain in the epigastrium and left side of the abdomen. His GP has treated him with amoxicillin and paracetamol, and the fever and abdominal pain had settled. However, he had developed the same symptoms after a week. On admission to a General Hospital his oral temperature was 38.6° Celsius, pulse 108 per minute regular, and BP 165/90. The ascending colon was palpable and tender, and his liver edge was palpable 3 cm below the right costal margin, and extremely tender. The following investigations were received within 24 hours.

Hb	12.0 g/dl	(14 – 17.5)	CRP	70 g/l	(<5 g/l)
MCV	90 fl	(80 – 96)	ESR	85 mm/h	(<20 mm/h)
MCHC	340 g/dl	(320 – 350)	AST	140 U/l	(<40)
WCC	12.0 X 10 ⁹ /l	(4 – 11)	ALT	420 U/l	(5 – 40)
(Neutrophils 75%)			ALP	210 U/l	(35 – 115)
			Bilirubin	40 µmol/l	(3 – 17)

Urine: No casts or significant cells; trace protein

1. What is your differential diagnosis?
2. What 6 investigations would you request?

Answers

Question 1

- (i) The triad of hypertension, marked hypokalaemia, and muscle weakness with wasting, appearing within a short period are characteristic features of Cushing syndrome due to ectopic ACTH secretion from tumours of the lung, pancreas, and medullary thyroid cancer, etc
- (ii) Important investigations in this patient include chest xray, ultrasound or CT scan of the abdomen, plasma cortisol and ACTH estimation, and urinary free cortisol estimation.
This patient's ultrasound examination of the abdomen revealed several metastatic liver nodules, and biopsy suggested small cell carcinoma. The CXR showed the source of the primary.
- (iii) The principal differential diagnosis of a patient having hypertension with hypokalaemia should include (a) hypertension and diuretic therapy (commonest cause); (b) Cushing syndrome due to a pituitary adenoma (Cushing's disease) or due to ectopic ACTH secretion, (c) adrenal adenoma or carcinoma; (d) glucocorticoid or ACTH therapy; (e) and conn syndrome. The commonest cause by far of Cushing syndrome is glucocorticoid or ACTH therapy.

Question 2

- (i) The probable diagnoses are (a) amoebic colitis and liver abscess (b) acute diverticulitis and liver abscess (c) viral hepatitis with either (a) or (b), and (d) viral hepatitis with diarrhoea caused by *Escherichia coli*, *Shigella*, *Salmonella* or *Giardia intestinalis*.
- (ii) (a) Blood cultures (e) Serological test for amoeba (eg complement fixation, ELISA)
(b) Abdominal ultrasound or CT scan (f) Stool culture
(c) Viral hepatitis serology screen (g) If a liver abscess is revealed, scan guided aspiration (and culture if indicated)
(d) Stool examination for *E histolytica*

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