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Case report

Pharmacokinetic and pharmacodynamic changes of Ivabradine induced by hypoalbuminemia: A case report.

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Abstract

Hypoalbuminemia is a common complication among hospitalized patients. Albumin is characterized by its non-specific binding to drugs, which makes hypoalbuminemia of concern among clinicians. Significant care should be applied to drugs of high protein binding capacity where hypoalbuminemia tends to cause pharmacokinetic changes and consequently, pharmacodynamic alterations. These changes require drug dose adjustment based on albumin level and kidney function as well. This case report highlights an explanation of events most likely occurring when acute hypoalbuminemia is recorded among critically ill patients. Ivabradine was a drug of choice to control inappropriate sinus tachycardia in a critically ill cancer patient where acute hypoalbuminemia was detected while kidneys were functioning properly (determined by eGFR) and liver enzymes including SGOT and SGPT showed normal values. The effect of ivabradine was easily detected by monitoring the heart rate in the intensive care unit. Pharmacokinetic changes associated with acute hypoalbuminemia observed in the case were associated with a decrease in heart rate which might be due to an increase in unbound/free fraction of ivabradine as a highly protein-bound drug, which led to an increase in the volume of distribution and hence increased activity of the drug as long as liver and kidney functions remained intact. The rapid increment in the fraction unbound drug was followed by an escalation of drug elimination where the heart rate increased, then returned to normal values. This is how our body maintains homeostasis. Integrating different pharmacokinetic parameters represents an essential step in decision-making about dose adjustment in hypoalbuminemia.

Keywords: Case report, Ivabradine, Hypoalbuminemia, Clearance

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1. Introduction

Hypoalbuminemia is considered to be a Vexing complication among hospitalized patients Representing a prevalence of almost 48% [1]. This is ultimately crucial as albumin is characterized by its non-specific binding to drugs which is of great importance. Acute hypoalbuminemia in clinical settings results in relative pharmacokinetic changes to drugs of high binding affinity to albumin. As a result, dose adjustment should be considered in relation to the route of drug elimination and baseline of albumin level when first administering these medications. For example, in patients with hypoalbuminemia and normal kidney functions in need to take ceftriaxone,
one approach used, was by administering 2g as an initial loading dose in hypoalbuminemia, then increasing the frequency of administration for maintenance dose to be 1g q8h while standard ICU dosing is 1g q12h [2]. This is attributed to the increased volume of distribution associated with hypoalbuminemia, especially in patients with normal kidney functions. Generally, data for dose adjustment are limited for a variety of medications with high binding affinity to albumin. Ivabradine is one of the drugs liable to pharmacokinetic changes and subsequent alterations in pharmacodynamic response. Ivabradine ultimately reduces heart rate through selective inhibition of the hyperpolarization-activated cyclic nucleotide-gated channels. FDA-approved ivabradine in heart failure management as it reduces the risk of hospitalization in symptomatic chronic heart failure patients classified as NYHA class II to III with resting heart rate ≥70 bpm and left ventricular ejection fraction ≤30% in case of contraindication to beta blockers or patients on maximally tolerated beta-blocker doses [3]. However, data from small prospective trials revealed the efficacy of ivabradine in reducing daytime heart rate in patients with inappropriate sinus tachycardia. Ivabradine is available in the form of tablets and solutions for oral administration and its elimination occurs through feces and urine; almost 4% is an unchanged drug. As ivabradine directly affects heart rate, the response could be easily identified and changes could be concluded by monitoring heart rate. This case report would illustrate how acute hypoalbuminemia resulted in a dramatic change in ivabradine serum level noticed through heart rate monitoring which to our knowledge represents a novel report to be added to the literature.

1. Case presentation

A 62-year-old male was admitted to the Emergency Department with dyspnea and hypoxia on room air saturation of 92%. The patient was recently diagnosed with a brain tumour with lung, liver, and bone metastases. However, neither a surgical approach nor chemotherapy was initiated before ICU admission. Past medical history included: type 2 diabetes mellitus, hypertension, and ischemic heart disease with 3 stents. Nevertheless, the exact timing of diagnosis of the mentioned comorbid conditions as well as home medications were not stated. Vital signs on admission included: Blood pressure 110/70 mmHg, heart rate 110 bpm, respiratory rate 28 breaths per minute, temperature 37.5°C, random blood glucose level 178 mg/dl. Physical examination and significant clinical findings revealed the following: by assessing Glasgow coma score, the patient was slightly confused and the heart rate was elevated. No murmurs, gallops, or rubs were auscultated. S1 and S2 heart sounds were heard clearly and were of normal intensity without any audible abnormalities. S1 was louder than

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S2 at the apex of the heart, and S2 was louder than S1 at the base of the heart, consistent with normal physiology. Pulmonology examination revealed hoarseness and wheezing.

Investigations included a chest X-ray showing right lung basal mass, lung metastases, and congestion. Doppler ultrasound showed deep venous thrombosis on the left upper limb. ECG revealed sinus tachycardia and no pathological Q waves. Abdominal and pelvic ultrasonography manifested that both kidneys had normal size and shape with normal echogenicity. No stones or hydronephrosis were indicated in the ultrasound. Sputum and blood culture had shown infection with *Acinetobacter baumannii*. Also, beta-D-glucan exhibited a high level; of 90 pg/ml (normal range: 30-59 pg/ml) and galactomannan level was 1 (normal value is < 0.5). These investigations together with clinical assessment and laboratory tests shown in **Tables 1 and 2** conveyed the following diagnosis: mediastinal syndrome with a left upper lung mass, brain tumor stage IV with metastases to lung, liver, and bone, DVT in the right upper limb, chest infection with *Acinetobacter baumannii* and fungal infection with *Aspergillosis* resulting in septic shock at day 3, according to systemic inflammatory host response (SIRS) criteria. Sepsis work-up includes: complete blood counts with differentiation, liver function tests, and coagulation studies including D- dimer level. Laboratory results indicated an increase in levels of WBCs, procalcitonin (PCT), CRP, PTT, and D-dimer. Challenges in diagnosis included MiniBAL which lasted for 5 days to be revealed. Although this was ordered from day 1, accessibility to it was on day 3, which caused a delay in starting appropriate antibiotics.

Table 1: Initial laboratory tests on admission day

Lab test (Normal value)	Hg (13-17) g/dl	Hct (40-50)%	Pt (150- 400) 10^9/L	WBCs (4-11) 10^9/L	BUN (6-24) mg/dl	S.Cr (0.7-1.3) mg/dl
Patient value	14.2	40	307	15.7	17.8	0.37
Lab test (Normal value)	CRP (0.3-1) mg/dl	Na (136-145) mEq/L	K (3.5-5) mEq/L	SGOT (<34) U/L	SGPT (14-59) U/L	PCT (<0.05) ng/ml
Patient value	128	133	3.6	20	26	1.02
Lab test (Normal value)	s.albumin (3.4-5.4) g/dl	D-dimer (0-0.5) mg/L	Ferritin (12-300) ng/mL	Uricacid (3.5-7.2) mg/dl	LDH (140-280) U/L	T. Ca (8.5- 10.3) mg/dl
Patient value	2.4	1.3	882	3.7	780	8.8
Lab test (Normal value)	TSH (0.3-4) mIU/L	T3 (2-4.4) pg/dL	T4 (0.93-1.7) ng/dL	INR (<1.1)	PT (11-13) sec.	PTT (25-35) sec.
Patient value	0.33	1.21	1.04	1.08	12.2	39

Hg= haemoglobin, Hct= haematocrit, plt=platelets, WBCs= white blood cells, BUN= Blood urea Nitrogen, S.cr= serum creatinine, CRP= C- reactive protein, SGOT= Serum Glutamic Oxaloacetic Transaminase, SGPT= Serum glutamic pyruvic transaminase, PCT= procalcitonin, LDH= lactate dehydrogenase, T.ca= total calcium, TSH= thyroid stimulatinghormone, T3= triiodothyronine, T4= thyroxine, INR= international normalized ratio, PT= prothrombin time, PTT= partial prothrombin time

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Table 2: Laboratory test results during intensive care unit stay.

	Day 1	Day 3	Day 5	Day 7	Day 9
Hg (g/dl)	14.2	13.3	12.4	12.6	11.2
Hct %	40.1	39	37	31	32
Pt 10^9/L	307	400	410	150	130
WBCs 10^9/L	15.7	20	21	36	29
BUN (mg/dl)	17.8	33	35	39	52
S.Cr (mg/dl)	0.37	1	1.1	1.1	1.1
CRP (mg/dl)	128.7	142	135	134	135
s.albumin (g/dl)	2.4	-	-	1.7	-

(-) means that the level was not detected on that day
Hg= haemoglobin, Hct= haematocrit, plt=platelets, WBCs= white blood cells, BUN= Blood urea Nitrogen, S.cr= serum creatinine, CRP= C- reactive protein, s.albumin

Hypoalbuminemia was also reported in laboratory tests. Actions taken regarding the patient's conditions included medications; illustrated in detail in **Table 3.** Concerning mediastinal syndrome, the patient got salbutamol, budesonide, dexamethasone, and torsemide. X-ray on day 3 indicated improvement of congestion, hence discontinuation of dexamethasone and torsemide. Concerning the management of DVT, enoxaparin was started at a therapeutic dose. Regarding sepsis, before culture and sensitivity tests were figured out, the patient started meropenem, levofloxacin, and linezolid together with hydrocortisone. Due to the observed increase in sepsis markers, the decision was to use tygecycline instead of linezolid on day 3 when the septic shock was manifested. The deterioration of the patient's condition determined by a decrease in blood pressure and low oxygen level resulted in the need for mechanical ventilation, thus midazolam and fentanyl were administered. Also, an initiation of norepinephrine was of great importance. Voriconazole was initiated as empirical before fungal markers results which were obtained on day 7. After blood culture had indicated sensitivity to colistin, it was initiated on day 9. The patientwas taking valsartan and bisoprolol for controlling blood pressure but discontinued on day 3, whereas, aspirin and clopidogrel for controlling ischemic heart disease were maintained from day 1. As for hypoalbuminemia recorded on admission, a dose of 50 ml/ 24hr was prescribed for three days starting from day 1. The main cause of hypoalbuminemia could be related to liver metastases and septic shock as well. For the management of sinus tachycardia, ivabradine was given with a dose of 5 mg/ 12 h, starting from day 1 monitoring of heart rate showed a normal level; 70 bpm till day 8. By day 9 there was a dramatic change in levels of serum albumin as it was observed to be 1.5 mg/dl and serum creatinine increased up to 1.1 mg/dl. Heart rate dropped to 40-60 bpm for two days then increased to 100 bpm for a day then returned normal 70 bpm. Albumin was given to compensate for hypoalbuminemia starting on day 9 with a dose of 50 ml/ 8 h and ivabradine dose was maintained at 5 mg /12 h (i.e., maintained on the same dosing). Follow-up of patient condition throughout ICU stay included monitoring vital signs and lab tests represented in **Table 2.** Sepsis markers did not show improvement despite adherence to the best evidence-based approach available. Also, the patient was

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maintained on mechanical ventilation. Unfortunately, the case died because of septic shock. A point to mention is that augmented clearance estimated on patient admission, which is correlated to critically ill cancer patients could affect antibiotic clearance resulting in subtherapeutic levels [(4)]. Hence, this can be a reason of failure pharmacologic intervention in managing sepsis in such settings, which is reported to be of high prevalence. Therapeutic drug monitoring would guide appropriate doses in this category particularly. In addition to this, voriconazole is one of the drugs depending on CYP2C19 in metabolism, which shows different variants between individuals. CYP2C19*17 polymorphism appears to play a major role as it results in subtherapeutic levels of voriconazole due to the extensive metabolism associated. Genetic testing would play an important role in determining the suitable dose for patients [(5)]. The mentioned two factors could be taken as take-home messages in managing such cases.

Table 3: Medication chart during hospitalization.

Drug	Dose	Route	Duration
Meropenem	1 gm/8 h	IV	Day 1 till end
Salbutamol	500 mcg /8 h	Inhalation	Day 1 till day 7
Budesonide	0.5 mcg/12 h	Inhalation	Day 1 till day 7
Ivabradine	5 mg / 12 h	Oral	Day 1 till day 12
Enoxaparin	60 mg/12 h	Subcutaneousinjection	Day 1 till day 12
Aspirin	75 mg/24 h	Oral	Day 1 till death
Clopidogrel	75 mg/24 h	Oral	Day 1 till death
Paracetamol	1 gm/ 8 h	IV	Day 1 till death
Levofloxacin	500 mg/24 h	IV	Day 1 and till day7
Linezolid	600 mg/12 h	IV	Day 1 and discontinued on day 3
Tygecycline	50 mg/ 12 h	IV	Day 3 till day 12
Colistin	LD: 9 M unit MD: 9 M unit individed doses twice daily	IV	Day 9 till day 12
Voriconazole	200 mg/ 12 h	IV	Day 3 till day 12
Dexamethasone	6 mg/ 12 h	IV	Day 1 till day 3
Hydrocortisone	6 mg / 6 h	IV	Day 3 till day 12
Torsemide	10 mg/ 24 h	Oral	Day 1 till day 3
Pantoprazole	40mg /24 h	IV	Day 1 till day day12
Valsartan	80 mg/12 h	Oral	Day 1 till day 3
Bisoprolol	5 mg/ 24 h	Oral	Day 1 till day 3
Midazolam	15 mg in 50 ml Rate 10 ml/h	IV Infusion	Day 3 till day 12
Fentanyl	0.1 mg Rate 5 ml/h	IV infusion	Day 3 till day 12
Albumin	50 ml/ 24 h 50 ml/ 8 h	IV infusionIV infusion	Day 1 till day 2 Day 7 till day 10
Norepinephrine	4 mg Rate 10 ml/h 4mg Rate 5 ml/h	IV infusion IV infusion	Day 3 till day 9 Day 9 till day 12

IV= intravenous

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2. Discussion

Ivabradine is a drug used for lowering heart rate through inhibition of cardiac pacemaker current. Ivabradine protein binding is almost 70% and Vd of 100 L, metabolized via CYP3A4 and excreted through feces and urine. In the mentioned case, the patient had cancer which is associated with arrhythmia. A correlation between cancer and arrhythmia is manifested by several mechanisms including metastasis to the myocardium, cardiac conditions inducing amyloidosis, and use of chemotherapeutic agents inducing cardiac toxicities [(6)].

Kidney function was impaired due to Acute kidney injury (AKI) associated with septic shock. For the management of sinus tachycardia, ivabradine was administered and the stated result could be explained by the following. Fluctuation in heart rate was recorded which may be due to an increase in the fraction of unbound drug upon acute hypoalbuminemia resulting in increased effect. As albumin is the protein controlling osmotic pressure, hypoalbuminemia would result in an increased volume of distribution [(7)]. After 3 days of albumin supplementation, heart rate returned to normal range. The most probable reason for explaining what had been observed concerning pharmacokinetic changes associated with drugs and not with chronic conditions and the patient's comorbidities is that these conditions were maintained constant during follow-up, thus ruling out that these conditions could have evoked the stated alteration. For instance, cancer as a chronic disease is linked to chronic alterations such as the development of arrhythmias, but not to the mentioned fluctuation. Another point should be figured out, tachycardia $\geq$ 90 bpm is one of SIRS criteria as a diagnostic criterion for sepsis, however, there is no available data correlating the mentioned fluctuation in heart rate to sepsis. In addition to this, work-up of sepsis including measuring procalcitonin and C-reactive Protein (CRP) levels and following the trend of white blood cells together with recording fever, showed almost the same values during the specified period of alteration [(8)].

Highly protein-bound drugs show a variation in their response secondary to hypoalbuminemia according to whether they have linear or non-linear kinetics. Ivabradine shows linear kinetics over an oral dose of 0.25 mg to24 mg [(9)]. What made ivabradine a typical drug to illustrate these pharmacokinetic and pharmacodynamic changes within this case and the response could be easily monitored through recording heart rate. Owing to the variation of one factor which was albumin level, whereas the stability of the others, the serum creatinine level, and liver function, the explanation of such adaptation was much easier. However, the availability of data regarding the management of such cases was very limited, making it hard to make a decision about changing the dose or to be maintained as such.

As known from the literature, the increase in the unbound/free fraction together with the unbound/free concentration which remains constant in hypoalbuminemia would affect the therapeutic outcome [(10)]. This case report may highlight the fact that the increase in free unbound drug is not the only consequence of hypoalbuminemia, but other factors could contribute to compensate for this increase, most probably clearance [(11)]. That would differ according to drug characteristics. The status of drug-eliminating organs and comorbid conditions affecting blood flow to drug-eliminating organs are factors of concern. Moreover, drug-related factors as the therapeutic index of the drug would affect the response to pharmacokinetic changes [(12)]. Increase in drug clearance attributed to increase in the fraction of unbound drug could be explained

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by the following: the increased free fraction could make more of the drug available for metabolism leading to increased metabolic activity and thus rapid elimination. In some cases, increase in the free fraction could result in the induction of the activity of drug-metabolizing enzymes or transporters leading to an increase in clearance to remove the excess drug from the body [13]. Also, it could be attributed to saturation to drug transporters or tubular reabsorption and increasing renal elimination [14].

The only accessible randomized control trial (RCT) tackled dose adjustment for certain antibiotics among two groups of patients and measured pharmacokinetic parameters to determine the appropriate dose among patients with normal albumin levels and patients with hypoalbuminemia [15]. Although, that study included only patients with normal kidney functions, results of that RCT included escalating initial dosing as well as maintenance doses of specified antibiotics for patients with hypoalbuminemia and normal kidney functions. Further studies should be implemented to provide proper dosing of highly protein-binding drugs with narrow therapeutic index in the presence of hypoalbuminemia. Another approach should be directed toward determining pharmacokinetic changes among patients with chronic kidney and liver diseases in the presence of hypoalbuminemia. To our knowledge, this is the first case report to correlate such pharmacokinetic alterations together with pharmacodynamic changes in clinical practice. Ivabradine tissue concentration, although could not be measured, it was almost predicted by monitoring its effect, HR. Discussion of the case outcomes showed a clear comprehensive approach and this is what strengthens this case report. In this case report, septic shock was considered a main limitation, further studies in non-septic patients could add to the literature about these pharmacokinetic changes. Also, the presence of liver metastasis, despite showing normal SGOT, SGPT, INR, and PT levels, might be a limitation in figuring out pharmacokinetic changes.

3. Conclusions

Hypoalbuminemia is a common and critical condition among hospitalized patients. Combining different pharmacokinetic parameters should be regarded as an essential step in decision-making about dose adjustment in hypoalbuminemia. Hypoalbuminemia leads to a significant increase in the fraction of free unbound drug which increases the volume of distribution. Depending on the route of elimination of drugs and patient comorbidities, response to hypoalbuminemia would exclusively differ. Further studies should be conducted to indicate the exact timing of these pharmacokinetic changes in different drugs.

Conflict of interest:

No conflict of interest

Data availability:

Data is available within the article.

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