

Suspected Adverse Drug Reactions Associated with Leukotriene Receptor Antagonists Versus First Line Asthma Medications: A National Registry-Pharmacology Approach

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Abstract

Aims. To determine the suspected adverse drug reaction (ADR) profile of leukotriene receptor antagonists (LTRAs: montelukast and zafirlukast) relative to first-line asthma medications short-acting beta agonists (SABA: salbutamol) and inhaled corticosteroid (ICH: beclomethasone) in the United Kingdom. To determine chemical and pharmacological rationale for the suspected ADR signals.

Methods. Properties of the asthma medications (pharmacokinetics and pharmacology) were datamined from the chemical database of bioactive molecules with drug-like properties, European molecular Biology laboratory (ChEMBL). Suspected ADR profiles of the asthma medications was curated from the Medicines and Healthcare products Regulatory Authority (MHRA) Yellow Card interactive drug analysis profiles (iDAP) and concatenated to the standardised prescribing levels (Open Prescribing) between 2018-2023.

Results. Total ADRs per 100,000 R_x ($P < .001$) and psychiatric system organ class (SOC) ADRs ($P < .001$) reached statistical significance. Montelukast exhibited the greatest ADR rate at 15.64 per 100,000 R_x . The low lipophilic ligand efficiency (LLE = 0.15) of montelukast relative to the controls may explain the promiscuity of interactions with off-target G-coupled protein receptors (GPCRs). This included the dopamine signalling axis, which in combination with bioaccumulation in the cerebrospinal fluid (CSF) to achieve C_{max} beyond a typical dose can be ascribed to the psychiatric side effects observed. Cardiac ADRs did not reach statistical significance but inhibitory interaction of montelukast with the MAP kinase p38 alpha (a cardiac protective pathway) was identified as a potential rationale for montelukast withdrawal cardiac effects.

Conclusion. Relative to the controls, montelukast displays a range of suspected system organ class level ADRs. For psychiatric ADR, montelukast is statistically significant ($P < .001$). A mechanistic hypothesis is proposed based on polypharmacological interactions in combination with CSF levels attained. This work further supports the close monitoring of montelukast for neuropsychiatric side effects.

NOTE: This preprint reports new research that has not been certified by peer review and should not be used to guide clinical practice.

Introduction

Asthma is a common respiratory condition worldwide. In the UK, 5.4 million people receive treatment, which equates to approximately 1 in 12 adults and 1 in 11 children. [1] This condition is responsible for approximately 3% of primary consultations, 200,000 bed days and 60,000 hospital admissions per year in the UK. [2] Asthma can affect people of all ages, and can range in severity, from very mild, infrequent wheezing, to severe life threatening, closure of the airways. [3] The economic cost of asthma in the UK is > £1bn p.a. which includes medication costs, healthcare professionals' time, diagnostic tests, and secondary care treatment. [4] The treatment of asthma, involves a stepwise approach, depending on the severity and level interventions required to manage symptoms. [5] Short-acting beta agonists (SABA) for example, salbutamol, is a 'reliever' therapy and the first line treatment. If asthma is uncontrolled with a SABA, an inhaled corticosteroid (ICS) for example, beclomethasone is prescribed as maintenance therapy. Should symptoms persist 'add-ons' can be given, for example, leukotriene receptor antagonists (LTRA). In the UK, montelukast and zafirlukast are licensed LRTAs (zafirlukast was discontinued in the UK on 31st March 2018). These drugs prevent the pro-inflammatory effects of cysteinyl leukotrienes at their receptors (*CysLT1*) found on the smooth muscles of bronchioles, which helps reduce the levels of inflammation and sensitivity of the airways to asthma triggers. [6]

All drugs can result in adverse drug reactions (ADRs) and can be classified by the DoTS system (dose of the drug, time course of the reaction, and susceptibility factors). [7] **Table S1** highlights the common adverse effects reported with asthma medications prior to this study. It should be noted that ICS side effects in **Table S1** are usually combined with inhalers may cause the same side effects to be reported for ICS so may not be causal for ICS alone. [8] Given the association of neuropsychiatric side effects with the LRTA, montelukast and its circulating metabolites, a pharmaco-epidemiology study is timely to explore the differential ADRs between LRTAs vs SABA vs ICH. [9-14]

Herein, we investigate LRTAs for suspected ADR signals reported between 2018-2023 with salbutamol and beclomethasone as comparators and explore the unique polypharmacology of the drugs for associations with statistically significant suspected ADRs.

Methods

Method databases

The Electronic Medicines Compendium (EMC), and the Chemical Database of bioactive molecules with drug-like properties European molecular Biology laboratory

(ChEMBL) databases were used to identify the physiochemical properties, pharmacokinetics, and pharmacology data of montelukast, zafirlukast, beclomethasone, salbutamol. [15-18]

Physiochemical properties

The physicochemical properties included molecular weight, pK_a , $tPSA$, hydrogen bond donors and acceptors, $clogD_{7.4}$, whether it is a P-glycoprotein substrate and the $clog_{10}P$. The pIC_{50} was calculated using the median IC_{50} of the target *homo sapien* protein for each respective drug. The lipophilic ligand efficacy (LLE) was calculated as follows: $LLE = pIC_{50} - clog_{10}P$ (**Table 1**). [18]

Blood-Brain Barrier (BBB) penetration

The prediction of BBB penetration was by determined by whether the physiochemical properties of the drugs meet requirements and thresholds to allow for penetration. Specifically, molecular weight < 450 Da, $tPSA < 90 \text{ \AA}$, neutral or basic characteristics based on pK_a , < 6 hydrogen bond donors and < 2 hydrogen bond acceptors, a $clogD_{7.4}$ between 1-3, and ability to be a P-glycoprotein substrate. The more requirements met, the higher predicted BBB penetration. [19]

Pharmacokinetic properties

The pharmacokinetic properties included bioavailability ($\%F$), half-life ($t_{1/2}$), T_{max} (time to reach the max concentration), C_{max} (peak plasma concentration), whether it was metabolised by a CYP P_{450} enzyme isoform, renal clearance (Cl), volume of distribution (V_d), total clearance (L/h), and plasma protein binding (PPB). C_{max} was converted from ng/mL to nM. EMC, DrugBank, PubChem, ChEMBL and wider literature were used to find pharmacokinetic data, by searching for “drug name” and “parameter required” (**Table 2**). [15-18, 20-25]

Pharmacological properties

The ChEMBL database was used to collect the human single protein target bioactivity data for montelukast, zafirlukast, beclomethasone and salbutamol. [18] The median IC_{50} values were used to determine a dependable pIC_{50} value (**Table 3**).

Prescribing data

Prescription data in primary care across England was curated from OpenPrescribing (August 2018 and September 2023). [26] Prescription items (R_x) were collated to standardise the suspected adverse drug reactions (ADRs) per 100,000 R_x to factor in variations in

prescription rates amongst the medications. A minimum of 100,000 R_x between 2018-2023 was an additional inclusion criterion.

Adverse drug reactions

Suspected ADR data was datamined from the Medicines and Healthcare products Regulatory Authority (MHRA) Yellow Card interactive Drug Analysis Profile (iDAP). Dates selected were January 2018 to November 2023 for single active constituents only. [27] System organ classes (SOC) with significant ADR rates across the medications and fatalities were selected. The ADR data required standardisation to allow for comparisons between the different drugs. ADRs per 100,000 R_x is a standard approach in signal hypothesis generation [18, 28-33] Drugs were compared to each other in terms of ADR SOCs (**Table S2** and **Table 4**) to determine statistically significant signals and where $P < .001$, high level group terms (HLGT) were additionally explored (**Table S3** and **Table 5**).

Results

Molecular properties

The structures of the medications studied are shown in **Figure 1**.

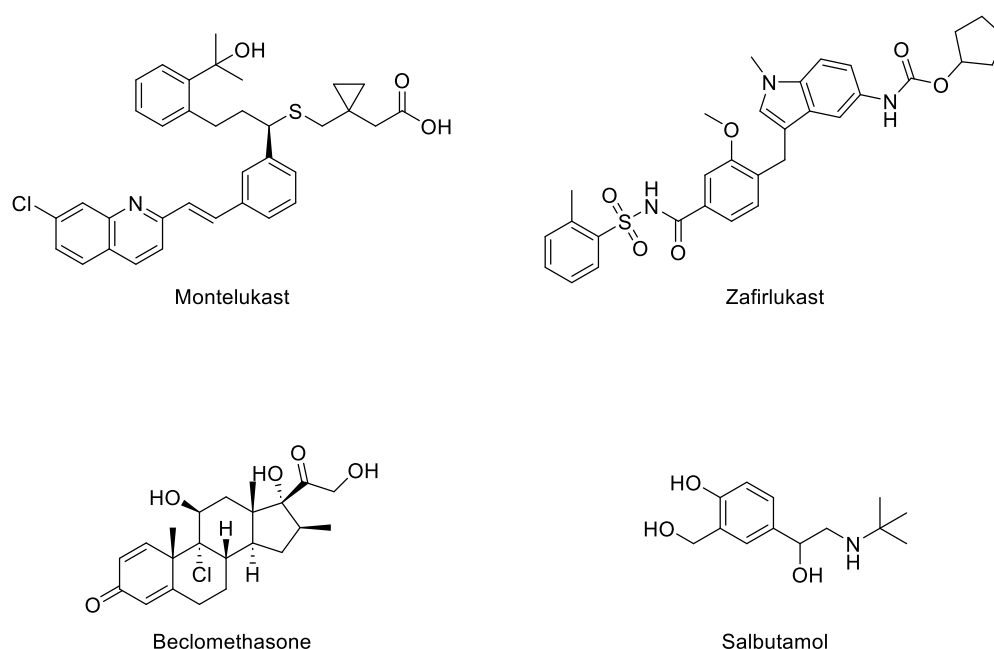


Figure 1. Structures of asthma medications studied (LRTAs: montelukast and zafirlukast, controls ICS: beclomethasone and SABA: salbutamol).

The physiochemical properties of montelukast, zafirlukast and the controls beclomethasone and salbutamol are displayed in **Table 1**.

Table 1. Physiochemical and BBB properties of montelukast, zafirlukast, beclomethasone and salbutamol.

<i>Variables</i>	<i>Montelukast</i>	<i>Zafirlukast</i>	<i>Beclomethasone</i>	<i>Salbutamol</i>
<i>pIC₅₀</i>	8.64	8.74	8.08	6.01
<i>clog₁₀P</i>	8.49	6.4	2.15	0.34
<i>LLE</i>	0.15	2.34	5.93	5.67
<i>MW (Da)</i>	586.2	575.69	408.92	239.31
<i>pK_a</i>	4.4 (acidic)	4.29 (acidic)	12.44 (neutral)	9.4 (basic)
<i>tPSA (Å)</i>	70.42	115.73	94.83	72.72
<i>HB acceptors</i>	4	7	5	4
<i>HB donors</i>	2	2	3	4
<i>Clog₁₀D_{7.4}</i>	5.8	5.46	2.15	-1.32
<i>P-glycoprotein Substrate</i>	Yes	Yes	Yes	Yes
<i>No. of BBB requirements met</i>	2	1	4	4

Montelukast was the most lipophilic drug (*clog₁₀P* = 8.49) and zafirlukast is the most potent (*pIC₅₀* = 8.74). Montelukast and zafirlukast both had an *LLE* significantly below 5 (0.15 and 2.34 respectively). The properties which met the requirements for BBB penetration are highlighted in green (**Table 1**). Salbutamol and beclomethasone met both the molecular weight requirement (<450 Da) and are either neutral or basic. Montelukast and salbutamol had a *tPSA* < 90 Å (70.42 Å and 72.72 Å respectively). No drugs had less than 2 hydrogen bond acceptors, however, all drugs had less than 6 hydrogen bond donors. Only beclomethasone had a

clogD_{7.4} between 1 and 3 (2.15). All drugs are P-glycoprotein substrates, but this mechanism declines with age.

Pharmacokinetic properties

Table 2. Pharmacokinetic properties of montelukast, zafirlukast, beclomethasone and salbutamol.

Variables	Montelukast	Zafirlukast	Beclomethasone	Salbutamol
<i>Bioavailability (%F)</i>	64%	100%	41%	24.8%
<i>Half-life (h)</i>	2.7 – 5.5	8 – 16	5.7	2.7 – 5.5
<i>T_{max} (h)</i>	3	3	0.7	0.17
<i>C_{max} (nM)</i>	656.77	442.95	86.46	1678.83
<i>CYP metabolism</i>	Yes: CYP3A4, CYP28C, CYP28B	Yes: CYP2C9	Yes: CYP430 3A	Yes: CYP 450
<i>Renal excretion</i>	< 0.2%	10%	negligible	272 ± 38 ml/min
<i>Volume of distribution (L)</i>	8 - 11	70	20	156 ± 38 (IV)
<i>Clearance (L/h)</i>	2.7	20	150	25.22
<i>PPB (%)</i>	99%	99%	87%	10%

The pharmacokinetic properties of the LTRAs and the controls are shown **Table 2**. Zafirlukast had the highest bioavailability of $F = 100\%$ (oral), while the lowest was salbutamol at 24.8%. The $T_{\max}$ was the same for montelukast and zafirlukast (3 h) but lower for beclomethasone and salbutamol (0.7 h and 0.17 h, respectively). All drugs were metabolised by cytochrome P₄₅₀ (CYP) familial isoforms. The V_d of salbutamol was highest (143.2 L) and the lowest was montelukast (8-11 L). Montelukast and zafirlukast had high plasma protein binding (PPB) of 99% compared to that of salbutamol at 10%.

Pharmacology properties

Table 3. Pharmacology properties of montelukast, zafirlukast, beclomethasone and salbutamol (nM).

Protein Group	Protein compound	Montelukast	Zafirlukast	Beclomethasone	Salbutamol
G Protein coupled receptors	Cysteinyl leukotriene receptor 1	2.3	8.7		
	Cysteinyl leukotriene receptor 2	27000	7397		
	Alpha-2a adrenergic receptor	3919			
	Alpha-2c adrenergic receptor	5279			
	Adenosine A1 receptor		>10000		
	Adenosine A3 receptor	434	1363		
	Beta-2 adrenergic receptor	3488			980
	Beta-3 adrenergic receptor	4300			
	Dopamine D1 receptor		>10000		
	Dopamine D3 receptor	7747			
	Delta opioid receptor	4795			
	Mu opioid receptor		>10000		
	Norepinephrine receptor	2689			
	Histamine H1 receptor		>10000		
	Neurokinin 2 receptor *	3822			
	Muscarinic acetylcholine receptor M1	8045			
	Muscarinic acetylcholine receptor M3	6626			
	Serotonin 2b (5T-HT2b) receptor	6256			
Transmembrane protein	Dopamine transporter	2601			
	Epidermal growth factor 1 erbB1	3197	5751		
MAPEG	Leukotriene C4 synthase	<5000			
	Prostaglandin E synthase		18100		
MAP	MAP kinase p38 alpha	856	6.4		
	MAP kinase ERK1		4376		
	MAP kinase ERK2		538		
CYP5	Thromboxane A synthase	1525	3810		
Src family kinases (SFks)	Tyrosine-protein kinase FYN	4702			
CYP 450	Cytochrome P450 2C8	1000			
SLC10 family of solute carrier proteins	Bile acid transporter		6500		

ABC superfamily transport proteins * APC transport family	Bile salt export pump		11100	16985	>1000000
	Multidrug resistance-associated protein 1		1300		
	Multidrug resistance-associated protein 2		7600		
	Multidrug resistance-associated protein 4		12100		>133000
	Canalicular multispecific organic anion transporter 1		58800		>133000
	Canalicular multispecific organic anion transporter 2		> 133000		>133000
	Group IVA cytosolic	Cytosolic phospholipase A2		85000	
Nuclear receptor family	Glucocorticoid receptor			8.2	
Protein superfamily	Thiosulfate sulfurtransferase				> 100000
Other	Epoxidase hydratase		2000		
C max (nM)		657	443	86	1679
Threshold (x 1.5)		985	664	130	2518
Legend	Empty - unknown	Clinically significant			

The pharmacology results show the clinically significant values in green with an inhibitory value below the C_{max} threshold (**Table 3**). A threshold was created (x1.5) to include off-target pharmacological activities that may fall outside the C_{max} due to differential dosing regimens. Montelukast was the most potent towards its target receptor, cysteinyl leukotriene receptor 1 (2.3 nM), then zafirlukast (8.7 nM). Montelukast showed potent interaction with off-target, adenosine A3 receptor (43 nM). Both montelukast and zafirlukast were potent towards off-target, MAP kinase p38 alpha (856 nM and 6.5 nM, respectively). Zafirlukast interacted with off-target, MAP kinase ERK2 (538 nM). Salbutamol was potent towards its on-target protein beta-2 adrenergic receptor (980 nM). Beclomethasone was potent towards its on-target receptor, glucocorticoid receptor (8.2 nM). Montelukast and zafirlukast were found to have potent interactions with additional off-target proteins (**Table 3**).

ADRs

Table 4. Summary of suspected ADR profiles of montelukast, zafirlukast, beclomethasone and salbutamol in the UK (the number in parentheses represents the standardisation to 100,000 Rx). *P*-values were calculated using a chi-squared test. Supporting data can be found in **Table S2**.

<i>Variables</i>	<i>Montelukast</i>	<i>Zafirlukast</i>	<i>Beclomethasone</i>	<i>Salbutamol</i>	<i>P</i>
Total prescriptions	18757214	1327	70250968	107619145	-
Total ADRs	2935 (15.64)	9 (678.22)	2327 (3.37)	1342 (1.24)	< .001
Fatalities	2 (0.01)	0 (0)	1 (0)	15 (0.01)	.95
Cardiac disorder	26 (0.13)	0 (0)	71 (0.1)	68 (0.06)	.98
Fatalities	0 (0)	0 (0)	0 (0)	0 (0)	-
<i>Palpitations</i>	23 (0.12)	0 (0)	59 (0.08)	24 (0.02)	.96
Gastrointestinal disorder	204 (1.08)	0 (0)	221 (0.31)	75 (0.06)	.56
Fatalities	0 (0)	0 (0)	0 (0)	0 (0)	-
<i>Abdominal pain</i>	17 (0.09)	0 (0)	3 (0.00)	1 (0)	.92
<i>Nausea</i>	39 (0.20)	0 (0)	37 (0.05)	9 (0)	.88
Nervous system disorder	322 ((1.71)	1 (72.88)	303 (0.43)	154 (0.14)	.39
Fatalities	0 (0)	0 (0)	0 (0)	0 (0)	-
<i>Headache</i>	72 (0.38)	0 (0)	67 (0.09)	19 (0.01)	.79
Psychiatric disorder	1542 (8.22)	0 (0)	174 (0.24)	73 (0.06)	< .001
Fatalities	2 (0.01)	0 (0)	0 (0)	1 (0)	.99
<i>Agitation</i>	34 (0.18)	0 (0)	6 (0)	1 (0)	.84
<i>Anxiety</i>	165 (0.87)	0 (0)	35 (0.04)	7 (0)	.46
<i>Depression</i>	82 (0.43)	0 (0)	7 (0)	4 (0)	.66
<i>Hallucinations</i>	42 (0.22)	0 (0)	1 (0)	3 (0)	.80
<i>Nightmare</i>	162 (0.86)	0 (0)	1 (0)	0 (0)	.42

<i>Suicidal ideation</i>	62 (0.33)	0 (0)	2 (0)	2 (0)	.72
<i>Completed suicide</i>	3 (0.01)	0 (0)	0 (0)	0 (0)	-
<i>Respiratory, thoracic, and mediastinal disorders</i>	125 (0.66)	0 (0)	587 (0.83)	528 (0.24)	.85
<i>Fatalities</i>	0 (0)	0 (0)	0 (0)	0 (0)	-

Total ADRs and psychiatric ADRs were found to be statistically significant at SOC level (**Table 4**). Further exploration of psychiatric ADRs at HLGT level are shown in **Table 5**. Montelukast provided a much higher ADR rate per 100,000 R_x in multiple organ class categories including cardiac disorder 0.13 (compared to 0.1 and 0.06 beclomethasone and salbutamol respectively), gastrointestinal disorder (1.08), nervous system disorders (1.71) and psychiatric disorders (8.22) per 100,000 R_x . Montelukast was the only drug with a completed suicide ADR rate at 0.01 per 100,000 R_x , whereas the others were zero. **Table 4** also shows that montelukast had a higher respiratory, thoracic, and mediastinal disorder than both beclomethasone and salbutamol but did not reach significance.

Table 5. Psychiatric System Organ Class> High Level Group Term (HLGT). Order of information presented: raw number of suspected reports, standardised to prescribing level in parentheses, fatalities in square brackets. HLGT reported where at least one drug has $n > 1$ report. P values reported where there were $n > 3$ reports. Supporting data can be found in **Table S3**.

<i>HLGT</i>	Montelukast	Beclomethasone	Salbutamol	<i>P</i>
Anxiety disorders and symptoms	275 (1.47)	58 (0.08)	22 (0.02)	0.28
Changes in physical activity	37 (0.20)	8 (0.01)	1 (0.00)	-
Cognitive and attention disorders and disturbances	6 (0.03)	1 (0.00)	0	-
Communication disorders and disturbances	15 (0.08)	1 (0.00)	0	-
Deliria (incl confusion)	19 (0.10)	5 (0.01)	3 (0.00)	0.92
Depressed mood disorders and disturbances	162 (0.86)	17 (0.02)	8 (0.01)	0.45
Developmental disorders NEC	1 (0.01)	0	0	-
Dissociative disorders	5 (0.03)	0	0	-
Disturbances in thinking and perception	76 (0.41)	5 (0.01)	6 (0.01)	0.69

Impulse control disorders NEC	4 (0.02)	0	0	-
Manic and bipolar mood disorders and disturbances	6 (0.03)	0	0	-
Mood disorders and disturbances NEC	182 (0.97)	25 (0.04)	5 (0.00)	0.41
Personality disorders and disturbances in behaviour	144 (0.77)	14 (0.02)	1 (0.00)	-
Psychiatric and behavioural symptoms NEC	65 (0.35)	7 (0.01)	1 (0.00)	-
Psychiatric disorders NEC	26 (0.14)	0	6 (0.01)	-
Schizophrenia and other psychotic disorders	12 (0.06)	0	1 (0.00)	-
Sexual dysfunctions, disturbances, and gender identity disorders	0	0	1 (0.00)	-
Sleep disorders and disturbances	411 (2.19)	30 (0.04)	15 (0.01)	0.12
Somatic symptom and related disorders	0	0	1 (0.00)	-
Suicidal and self-injurious behaviours NEC	96 (0.51) [2]	3 (0.00)	2 (0.00)	0.60

Discussion

Total ADRs and fatalities

Zafirlukast was discontinued in 2018 due to commercial reasons. [34] This led to the drug not meeting the requirements for the inclusion criteria for the ADR/prescribing data collection as it had less than 100,000 R_x and therefore excluded from the discussion of addressing ADRs and fatalities.

Amongst all the drugs, montelukast had the highest ADR rate at 15.64 per 100,000 R_x , followed by beclomethasone at 3.37 and salbutamol at 1.2. Montelukast had significantly lower LLE compared to both beclomethasone and salbutamol (0.15 compared to 5.93 and 5.67) (**Table 1**). This implies greater promiscuity, and the data corroborates this, as montelukast potentially inhibits two off-target proteins (**Table 3**). The highest rate for fatalities across the drugs was shared by both montelukast and salbutamol (0.01 per 100,000 R_x).

Psychiatric ADRs

All SOC ADRs analysed were found to not reach statistically significant except for psychiatric ADRs (**Table 4**). Montelukast ($P < .001$) provided the highest ADR rate at 8.22 per 100,000 R_x , which is logarithmically higher than the controls, beclomethasone, and salbutamol (0.24 and 0.06 per 100,000 R_x , respectively).

Further data-mining beyond SOC to HLGs (**Table 5**) revealed emerging trends between montelukast and the controls but in all cases did not reach statistical significance ($P > .001$). Anxiety disorders and symptoms (275 vs 70 reports for montelukast vs controls respectively), depressed mood disorders (162 vs 25 reports for montelukast vs controls respectively), disturbances in thinking and perception (76 vs 11 reports for montelukast vs controls respectively), mood disorders (182 vs 30 reports for montelukast vs controls respectively), sleep disorders (411 vs 45 reports for montelukast vs controls respectively), and suicidal and self-injurious behaviours (96 vs 5 reports for montelukast vs controls respectively), showed clear trends with higher reports for montelukast for both directly suspected ADRs and when standardised to prescribing levels compared to the controls. Furthermore, two fatalities within the suicidal and self-injurious category emerged for montelukast compared to the controls (0 for both salbutamol and beclomethasone).

A previous study compared the side effects of antidepressants and immune modulators including montelukast, in human cell lines. Montelukast had a similar side effect profile to the atypical antidepressant, bupropion, which is a dopamine and norepinephrine reuptake inhibitor. [35] Montelukast impacts dopamine levels at a cellular level, despite not being pharmacologically relevant at the protein level based on a single dose C_{max} (**Table 3**). However, physiochemical data can only predict to a certain extent. Another study found that montelukast (at the recommended dose of 10 mg) was discovered in the cerebrospinal fluid (CSF) at a therapeutic dose. The central nervous system (CNS) was then evaluated afterwards to show that montelukast had penetrated the BBB significantly which differs from the predicted BBB in **Table 1**. [36] Furthermore a study of neuropsychiatric events in children, adolescents, and young adults taking montelukast found that montelukast accumulates in the CSF. [37]. This accumulation at levels sufficient to impact the dopamine receptor (7.7 μM , **Table 3**) may potentially explain some of the psychiatric side effects.

Cardiac ADRs and fatalities

Montelukast had a higher cardiac ADR rate at 0.13 per 100,000 R_x compared to both beclomethasone and salbutamol (**Table 4**). Suspected montelukast induced heart palpitations, were significantly higher (0.12) in comparison with beclomethasone and salbutamol (0.08 and 0.02 per 100,000 R_x).

Montelukast is only usually added to asthma treatment if a patient has not responded to first line treatment with salbutamol with regular low dose inhaled corticosteroid (beclomethasone) has not been successful as an alternative to an increased dose of inhaled corticosteroid, allowing management of symptoms via an alternative pharmacological pathway. [38-39]

Montelukast has off target interactions with Adenosine A3 receptor and MAP kinase p38 alpha. The interaction with MAP kinase p38 alpha may be a cause of the cardiac effects. The p38 MAPK pathway plays an integral role in cardiac contractility and cardiac remodelling, and thus inhibiting this protein may be a potential cause for the cardiac ADRs resulting with montelukast. [40] Cessation of montelukast was considered a possible trigger in a 53-year-old male endurance athlete who presented with a two-week history of symptomatic ventricular ectopics, confirmed by ECG and 24-hour tape. Other investigations were considered normal with no alternative identifiable causes for the arrhythmias which resolved 24 hours after re-starting the montelukast. [41]

Montelukast also inhibits adenosine A3 receptor this has a significant role in myocardial infarction and atherosclerosis. Adenosine A3 receptor has cardioprotective characteristics which montelukast inhibits, which may make patients susceptible to deleterious cardiac affects. [42]

Gastrointestinal disorders and site of administration ADRs

Montelukast exceeded both beclomethasone and salbutamol's suspected gastrointestinal (GI) ADR rates per 100,000 R_x at 1.08 versus 0.31 and 0.06, respectively (**Table 4**). Montelukast caused a greater portion of GI ADRs which may be attributed to montelukast containing a lactose formulation, which certain patients may not respond well to.

There are directions for prescribers to assess whether the patient can tolerate this montelukast formulation by considering hereditary lactose conditions. [15] No fatalities were observed during this study for GI ADRs with non-serious ADRs reported. For abdominal pain, montelukast had a rate of 0.09 per 100,000 R_x whereas beclomethasone and salbutamol had zero. This is consistent to known side effects with montelukast (**Table S1**), therefore corroborating the validity of the approach using Yellow Card registry data. [8]

Nervous system ADRs

Montelukast had the highest ADR rate at 1.71 per 100,000 R_x , whereas beclomethasone and salbutamol were lower (0.43 and 0.14, respectively). These ADRs share a similar background to psychiatric ADRs with BBB penetrability involved and affecting the dopamine axis. [35-36] Headaches are associated with montelukast at 0.38 per 100,000 R_x whereas for 0.09 and 0.01 for salbutamol and beclomethasone which was validated with comparison to known side effects of montelukast. [8]

Limitations

A limitation of this study is that zafirlukast was discontinued in 2018 resulting in only 1 year of prescribing data during the 5-year timeline of this study. The reason for the discontinuation of zafirlukast was reported as distribution issues rather than safety concerns of the drug.

The MHRA Yellow Card interactive Drug Analysis Profile provides all the suspected ADRs that have been self-reported by both healthcare professionals and patients which is known to lead to a high degree of underreporting of side effects. This underreporting reduces the power of comparisons made across the drugs.

It should also be noted that some drugs are in the public mindset (e.g. montelukast) when announcements are made regarding potential side effects, this may cause an uptick in reports generated, in comparison to a drug (e.g. salbutamol) which is a well-established first line treatment that may not be reported at the same rate.

Causality does not need to be established before reporting to the Yellow Card scheme, therefore, the drug in question may not be the cause of the effect but rather other factors (polypharmacy, QoL, comorbidity), leading to the misrepresentation of the ADRs. Consequently, an assertive claim about the drug and which ADR it may cause, based alone on the MHRA yellow card scheme is not possible. However, trends and signal detection are possible.

ADRs used in this study are reported between January 2018 and November 2023, whilst the prescription data was available from August 2018 to September 2023. This does not affect the standardisation of drugs as the time frame remains consistent but may not appropriately reflect the drugs across the full 5 years of the study.

Conclusion

Based on the data observed in this study, montelukast has shown a wide range of suspected ADRs, ranging from cardiac, gastrointestinal, nervous system, and psychiatric effects. The physiochemical data showed a poor prediction of the BBB penetration of montelukast, but evidence from the literature suggest that montelukast does penetrate the BBB and accumulate in the CSF.

The research approach employed in this study was validated with the rediscovery of known montelukast ADRs. In particular, the elevated levels of nervous system and psychiatric disorders reported with montelukast are consistent with the MHRA field notice about adverse effects associated with montelukast. [43]. Montelukast has been associated with mood changes, depression, aggression, hallucinations, and suicidal thoughts and this work further supports these

neuropsychiatric findings and a potential pharmacological rationale via interaction with the dopamine GPCR axis through CSF accumulation.

Cardiac ADRs associated with montelukast have a tentative relationship with the pharmacological profile which supports the inhibition of off-target proteins that have an association cardiac ADRs.

The research demonstrated a new perspective that combines pharmacovigilance registries and chemical-pharmacological data to understand the potential causes of the ADRs of LTRAs.

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